Seventeenth Annual Meeting — American College of Chest Physicians
Ambassador Hotel, Atlantic City, New Jersey, June 7-10, 1951

VOLUME XIX NUMBER 2

DISEASES

of the

CHEST

OFFICIAL PUBLICATION

PUBLISHED MONTHLY

FEBRUARY
1951

EXECUTIVE OFFICE, 500 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS
PUBLICATION OFFICE, ALAMOGORDO ROAD, EL PASO, TEXAS

Entered as Second Class Matter August 18, 1936, at the Postoffice at El Paso, Texas
Under the Act of Congress of August 12, 1912.
Copyright, 1951, by the American College of Chest Physicians

Where the science of treatment is first

ROCKY GLEN SANATORIUM

McCONNELSVILLE, OHIO

FOR THE MEDICAL AND SURGICAL TREATMENT OF TUBERCULOSIS

LOUIS MARK, M.D., Medical Director, 677 North High Street, Columbus, Ohio

HARRY MARK, Superintendent — **MRS. H. A. PHILLIPS,** Asst. Superintendent

HENRY BACHMAN, M.D., Resident Medical Director

MICHAEL L. MICHAELIS, M.D., Res. Phys. — **FELIX BACHMANN, M.D.,** Res. Phys.

L. CHANDLER ROETTIG, M.D., Surgeon — **EARL W. DENNY, D.D.S.,** Attending Dentist

Beautiful Surroundings — **Reasonable Rates**

THE CALIFORNIA SANATORIUM

BELMONT, CALIFORNIA

Located in the well-known sunny belt of the Peninsula, about thirty miles south of San Francisco. Large park, semi-tropical grounds, walks, especially laid out for graduated exercise.

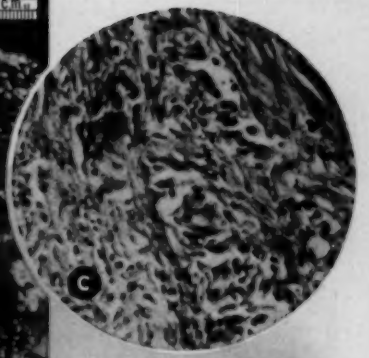
Not too hot in summer — not too cold in winter.

Physicians on duty day and night — Graduate nurses.

THOMAS B. WIPER, M.D., Director and Consultant in Thoracic Surgery

W. H. TORRE, M.D., Resident Clinician — **ALLEN B. LILIENTHAL, M.D., Clinician**

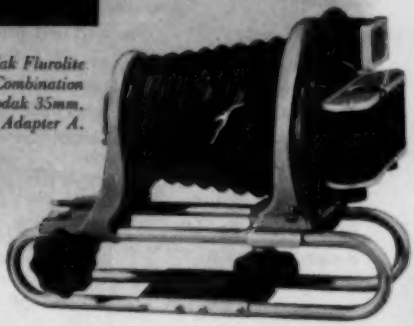
SAN FRANCISCO OFFICE: 536 MASON STREET — PHONE DOUGLAS 2-5793



Reproductions A *and* B *show gross aspects of diseased lung after pneumonectomy. Reproduction* C *shows photomicrograph made from histological section of affected lung.*

Illustration D *shows setup of Kodak Flurolite Enlarger fitted with Camera components for the photography of gross specimens.*

Kodak Flurolite Camera Combination with Kodak 35mm. Film Adapter A.



Picture the patient

. . . Routine procedure in more and more situations

Here are instruments ideally suited to the widening demands of medical photography.

Exactly framed, needle-sharp pictures are routine with Kodak Flurolite Camera Combination and Kodak Flurolite Enlarger assembled for photographing gross specimens . . . thanks to the revolving swing back, the easy adjustments, the long bellows draw.

The Camera Combination uses 2¼x3¼-inch sheet film . . . is easily converted to accept 35-millimeter roll film. Interchangeable Kodak Ektar Lenses in Kodak Flash Supermatic Shutters assure brilliant results—black and white or full color . . . flood or flash.

Additional uses of Kodak Flurolite Enlarger (with accessories): Copying, slide-making, cine-titling, photomicrography, and microfilming. See Kodak Flurolite Camera Combination and Kodak Flurolite Enlarger at your photographic dealer's . . . or write for further information to Eastman Kodak Company, *Medical Division*, Rochester 4, N. Y.

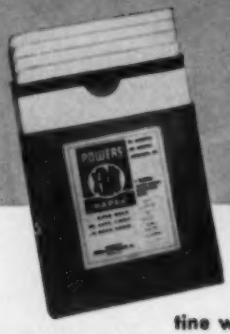
Kodak products for the medical profession include:

X-ray films, screens, and chemicals; electrocardiographic papers and film; cameras and projectors—still- and motion-picture; enlargers and printers; photographic film—full-color and black-and-white (including infrared); photographic papers; photographic processing chemicals; microfilming equipment and microfilm.

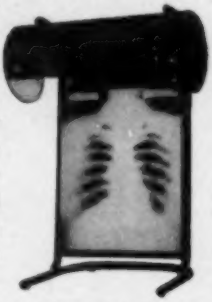
Serving medical progress through Photography and Radiography

Kodak
TRADE-MARK

POWERS X-RAY PAPER REDUCES COSTS 50% OR MORE!



For most routine work, radiographs of high quality can be made at less than half the usual cost with Powers X-Ray Paper. That is why more and more hospitals are using *both* paper and celluloid base film in their X-Ray departments. Techniques differ only slightly.



Proven in use for over 16 years, Powers X-Ray Paper comes in standard sheet sizes, or perforated rolls for use with the Powers Magazine Cassette.

Let us show you in detail how you can effect substantial savings with Powers X-Ray Paper. Write for complete information and literature.

POWERS X-RAY PRODUCTS, INC.

Reg. U.S. Pat. Off.
POWERS X-RAY PRODUCTS
Group Radiography
Glen Cove, Long Island, N. Y.

Medical Book Service Department

Announces a New Book

In both the English and Spanish Editions

SURGICAL EXTRAPLEURAL PNEUMOTHORAX

BY DONATO G. ALARCON, M.D., F.C.C.P., MEXICO CITY, D. F.

"If you are fortunate enough to have been among the numerous guests who have enjoyed the distinguished author's courteous hospitality, you will have seen in his Sanatorium at Huipulco, part of the cases on which the following pages are based, you will have been assured of his trustworthiness and scientific recititude, and, if your visit was not too short, you will have understood why a method that has failed in so many other places is successful at Huipulco."

—Leo Eloesser, M.D., F.C.C.P.

"Both Internists and Surgeons who care for the Tuberculous will do well to give this detailed series careful study. Dr. Alarcon's results, and his technique in achieving them, will go far toward returning this important surgical procedure to the place in the treatment of pulmonary tuberculosis that it deserves."

—Frank Stephen Dolley, M.D., F.C.C.P.

PRICE $8.00

- - - - - - - - - - - - - - - -

American College of Chest Physicians
500 North Dearborn Street,
Chicago 10, Illinois

Gentlemen: Enclosed herewith please find my remittance in the amount of $8.00. Kindly send me a copy of "Surgical Extrapleural Pneumothorax" by Donato G. Alarcon, M.D., F.C.C.P.

NAME.....

ADDRESS.....

CITY.....

STATE.....

DISEASES *of the* CHEST

OFFICIAL PUBLICATION
OF THE
AMERICAN COLLEGE OF CHEST PHYSICIANS

EDITORIAL BOARD

JAY ARTHUR MYERS, M.D.
Chairman
Minneapolis, Minnesota

ANDREW L. BANYAI, M.D.
Milwaukee, Wisconsin

RICHARD H. OVERHOLT, M.D.
Brookline, Massachusetts

CHARLES M. HENDRICKS, M.D.
El Paso, Texas

HENRY C. SWEANY, M.D.
Jacksonville, Florida

ASSOCIATE EDITORS

MILTON W. ANDERSON, M.D.....Rochester, Minnesota
EDWARD P. EGLEE, M.D.....New York, New York
SEYMOUR M. FARBER, M.D.....San Francisco, California
EDWARD W. HAYES, M.D.....Monrovia, California
PAUL H. HOLINGER, M.D.....Chicago, Illinois
CHEVALIER L. JACKSON, M.D.....Philadelphia, Pennsylvania
HOLLIS E. JOHNSON, M.D.....Nashville, Tennessee
EDGAR MAYER, M.D.....New York, New York
ALTON OCHSNER, M.D.....New Orleans, Louisiana
GEORGE G. ORNSTEIN, M.D.....New York, New York
J. WINTHROP PEABODY, M.D.....Washington, D. C.
LEO G. RIGLER, M.D.....Minneapolis, Minnesota

CORRESPONDING ASSOCIATE EDITORS

Donato G. Alarcon, M.D., Mexico
Adrian Anglin, M.D., Canada
Jose Ignacio Baldo, M.D., Venezuela
Etienne Bernard, M.D., France
Miguel Canizares, M.D., Philippine Is.
Manoel de Abreu, M.D., Brazil
Lopo de Carvalho, M.D., Portugal
Sir Alexander Fleming, England
Ovidio Garcia Rosell, M.D., Peru
Fernando D. Gomes, M.D., Uruguay
Affonso MacDowell, M.D., Brazil
David P. Marais, M.D., South Africa
Amadeo V. Mastellari, M.D., Panama
Gustav Maurer, M.D., Switzerland
Andre Meyer, M.D., France
Papken S. Mugriditchian, M.D., Lebanon
Antonio Navarrete, M.D., Cuba
Juda M. Pauzner, M.D., Israel
Hector Orrego Puelma, M.D., Chile
Raul F. Vaccarezza, M.D., Argentina
Raman Viswanathan, M.D., India
Harry W. Wunderly, M.D., Australia
Attilio Omodei Zorini, M.D., Italy

Antonio A. Adames, M.D.
Assistant Editor

Jay Arthur Myers, M.D.
Editor-in-Chief

Arthur Q. Penta, M.D.
Assistant Editor

EXECUTIVE OFFICE
500 North Dearborn Street, Chicago 10, Illinois
MURRAY KORNFELD, *Managing Editor*

VOLUME XIX FEBRUARY 1951 NUMBER 2

CONTENTS:

SURGICAL REPAIR OF MITRAL INSUFFICIENCY 125
(A Preliminary Report)
Charles P. Bailey, M.D., Thomas J. E. O'Neill, M.D.,
Robert P. Glover, M.D., William L. Jamison, M.D. and
Hector P. Redondo Ramirez, M.D., Philadelphia, Pennsylvania

SERUM CONCENTRATIONS OF PARA-AMINOSALICYLIC ACID (PAS) PRODUCED BY VARIOUS FORMS OF PAS 138
Douglas K. Duncan, M.D., David T. Carr, M.D., Rochester, Minnesota
Karl H. Pfuetze, M.D., Cannon Falls, Minnesota and
Marschelle H. Power, Ph.D., Rochester, Minnesota

PATHOLOGY OF TUBERCULOSIS TREATED WITH STREPTOMYCIN: A REVIEW OF 34 CASES 145
Oscar Auerbach, M.D., Leo Weiss, M.D. and
Grant N. Stemmermann, M.D., Staten Island, New York

THE EFFECT OF HEAT ON STREPTOMYCIN AND PARA-AMINOSALICYLIC ACID IN TUBERCULOSIS CULTURE MEDIUM 158
Margaret C. Drummond, M.S., George T. Lewis, Ph.D. and
Martin M. Cummings, M.D., Chamblee, Georgia

SPONTANEOUS RUPTURE OF THE ESOPHAGUS 165
M. Eugene Flipse, M.D., Miami, Florida

DIFFUSE BILATERAL FIBROCYSTIC DISEASE OF LUNGS (HONEY-COMB LUNGS) 190
Leroy Hyde, M.D., Bernard Hyde, M.D. and
Charles Pokorny, M.D., Los Angeles, California

BRONCHOGENIC CARCINOMA MASKED BY PULMONARY TUBERCULOSIS: CASE REPORT 201
J. R. Phillips, M.D., and J. W. Morrison, M.D., Houston, Texas

MEDIASTINAL TERATOMA 209
Frank T. Fralick, M.D., Rome, Georgia and
Hugh S. Weisman, M.D., Toronto, Canada

CYSTS OF THE PLEURA 221
Wallis L. Craddock, M.D., Fort Logan, Colorado

A CASE OF PLASMACYTOMA OF THE LUNG 227
M. Kuley, M.D. and O. Kuntman, M.D., Istanbul, Turkey

OBSTRUCTIONS OF SUPERIOR VENA CAVA 234
L. H. Ferguson, Jr., M.D. and Wm. A. Werner, M.D., St. Louis, Missouri

SEVENTEENTH ANNUAL MEETING OF THE COLLEGE 237

MINUTES OF THE SEMI-ANNUAL MEETING, BOARD OF REGENTS 237

MEETING OF THE EDITORIAL BOARD, DISEASES OF THE CHEST 242

COMMITTEE ON NOMINATIONS 243

PRIZE ESSAY AWARD 243

COLLEGE CHAPTER NEWS 244

COLLEGE NEWS NOTES 245

OBITUARY: Burt Russell Shurly 247

MEDICAL SERVICE BUREAU 248

Entered as second class matter, August 18, 1936, at the postoffice at El Paso, Tex., under the Act of Aug. 24, 1912.

Annual Subscription: United States of America $8.50
Foreign Countries $9.50

Introducing the new

KELEKET KRF-3!

for the modest budget...

A Single Tube .... complete diagnostic X-ray combination

Shifting from radiography to fluoroscopy or back again, is extremely simple. As shown, the X-ray tube during horizontal (or vertical) fluoroscopy is slipped into bracket located beneath the table. Thus, automatically centered, tube and screen move freely and easily regardless of table tilt. Tube is positioned over table for radiographic technics.

The
KELLEY - KOETT
Manufacturing Company
2142 West Fourth Street
Covington, Kentucky

WRITE FOR FREE DETAILED LITERATURE

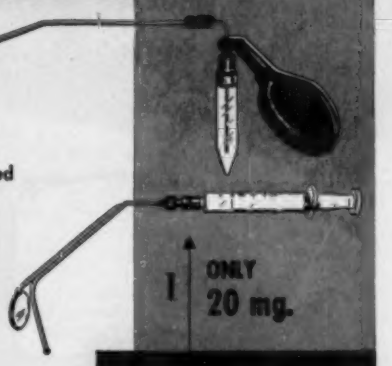
Keleket... The oldest name in X-ray

Safe, Effective Surface Anesthesia
FOR BRONCHOSCOPY AND BRONCHOGRAPHY

Two New Technics

Application by Micro-Atomizer (Carabelli)[1]

Only 20 mg. of Pontocaine hydrochloride produce effective surface anesthesia for bronchoscopy and bronchography, as shown by Dr. A. Carabelli in over 500 consecutive unselected cases. Administered by means of a simple "one-hand" micro-atomizer and mirror-cannula[2] 8 cc. or less of 0.25 per cent Pontocaine hydrochloride solution plus 8 minims of epinephrine 1:1000 will satisfactorily anesthetize the pharynx, larynx, trachea and bronchi.



1 ONLY 20 mg.

Penetrating and Prolonged Surface Anesthesia...

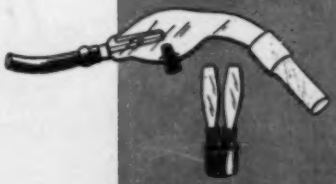
PONTOCAINE® HYDROCHLORIDE

Application by Nebulization (Miller et al.)[3]

A technic of nebulization (using De Vilbiss No. 40 nebulizer) of Pontocaine hydrochloride has been used successfully by Miller, Mann and Abramson in 50 cases of bronchography and 20 cases of bronchoscopy.

Only 8 cc. of Pontocaine 0.5 per cent solution plus 8 minims of epinephrine 1:1000 are introduced into the nebulizer. The procedure involves the absorption of 10 mg. (i.e., 2 cc. of 0.5 per cent solution) or less of Pontocaine hydrochloride.

2 ONLY 10 mg.



0.5% Solution, bottles of ½ oz. and 2 oz.

2% Solution, bottles of 1 oz. and 4 oz.

1. Carabelli, A.: Diseases of the Chest, 15:332, May, 1949 (167 cases; balance to be published).
2. Available from George P. Pilling & Son, Co., 3451 Walnut Street, Philadelphia 4, Pa.
3. Miller, J. E., Mann, F., and Abramson, H. A.: Diseases of the Chest, 16:408, Oct., 1949.

Winthrop-Stearns INC. New York N.Y.

Pontocaine, trademark reg. U. S. & Canada, brand of tetracaine

DOUBLY EFFECTIVE

in acute upper respiratory infections

In the treatment of chronic sinusitis and the acute sinus complications of coryza, Bacitracin-Nasal affords a dual approach.

It supplies bacitracin, effective against many gram-positive pathogens which inhabit the nose and accessory nasal sinuses.[1] Administered by spray or by aerosol inhalation, a solution of bacitracin has been reported to reduce the severity and duration of sinus infections.[2,3]

The presence of desoxyephedrine in Bacitracin-Nasal aids in improving nasal ventilation and reduces patient discomfort for prolonged periods.

Reconstituted by the pharmacist just prior to being dispensed, Bacitracin-Nasal contains bacitracin, 250 units per cc., and 0.25% desoxyephedrine in an approximately isotonic, rose-scented aqueous vehicle. It is available on prescription at all pharmacies in 15 cc. bottles together with dropper.

1. Prigal, S. J.: Bacteriologic and Epidemiologic Approach to the Treatment of Respiratory Infections with Aerosols of Specific Antibiotics, Bull. N. Y. Acad. Med. 26:282 (Apr.) 1950.

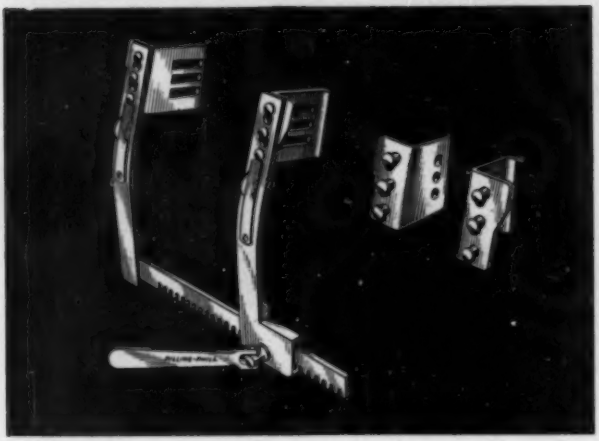
2. Stovin, J. S.: The Use of Bacitracin in the Treatment of Sinusitis and Related Upper Respiratory Infections, New York Physician 32:14 (July) 1949.

3. Prigal, S. J., and Furman, M. L.: The Use of Bacitracin, a New Antibiotic, in Aerosol Form; Preliminary Observations, Ann. Allergy 7:662 (Sept.-Oct.) 1949.

C.S.C. Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION • 17 E. 42ND ST. • NEW YORK 17, N.Y.

Authentic Instruments
FOR THE THORACIC SURGEON



BURFORD MODIFICATION OF THE
FINOCHIETTO RIB SPREADER

Thoracic surgeons look to Pilling for the new and important instruments in their special field. Since 1814, leaders in this field have consulted Pilling and designed instruments to fit their exacting requirements, confident in their knowledge that Pilling craftsmen would create the instruments they desired.

A fine example of Pilling craftsmanship is the Finochietto Rib Spreader, originally designed by Professors Henrique and Ricardo Finochietto of Buenos Aires. Now, the modification of this popular instrument by Thomas H. Burford, M.D., Barnes Hospital, St. Louis, provides even greater versatility. By properly switching the two pairs of interchangeable blades, the instrument can be used as medium or large size, or combinations of one large and one small blade. The shafts are also curved to conform to body curvature, thus keeping the spreader out of the operator's way.

ORDER instruments direct from

George P. Pilling and Son Company

3451 WALNUT STREET
Philadelphia

SAROT
Bronchial Clamp
Available in pairs—right and left

SAROT
Intra-Thoracic Artery Clamp

SATINSKY
Scissors

SATINSKY
Vena Cava Clamp

A Standing Invitation: When in Philadelphia, visit our modern sales rooms and manufacturing plant. Free parking on our private lot.

INSTRUMENTS BY Pilling

PILLING FOR PERFECTION in surgical instruments

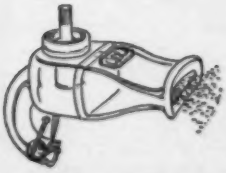
BACK on the job, back to activity is now a reality for many chronic asthmatics, thanks to an effective new bronchodilating powder. It is NORISODRINE Sulfate, supplied in multiple-dose cartridges, for inhalation therapy with the AEROHALOR.

The asthmatic simply inhales orally three or four times and the attack usually ends quickly. Effective against both mild and severe asthma, NORISODRINE has been proved by clinical investigation.[1,2] Proper administration results in few and usually minor side-effects.

Before prescribing this potent drug, however, please write to Abbott Laboratories, North Chicago, Illinois, for literature. This explains how to determine individual dosage and the precautions to be observed.

NORISODRINE Sulfate powder 10% and 25% is available in multiple-dose, disposable AEROHALOR* Cartridges. Abbott

*Trade Mark for Abbott Sifter Cartridge.



Norisodrine sulfate powder

(ISOPROPYLARTERENOL SULFATE, ABBOTT)

For use with the AEROHALOR,* Abbott's Power Inhaler

Always Ready for Use When the Need Arises

1. Krasno, L. R., Grossman, M. I., and Ivy, A. C. (1949), The Inhalation of 1-(3',4'-Dihydroxyphenyl)-2-Isopropylaminoethanol (Norisodrine Sulfate Dust), J. Allergy, 20:111, March. 2. Krasno, L. R., Grossman, M., and Ivy, A. C. (1948), The Inhalation of Norisodrine Sulfate Dust, Science, 108:476, October 29.

NOW IS THE TIME .....

To Make Hotel Reservations
for the

SEVENTEENTH ANNUAL MEETING
American College
Of Chest Physicians

AMBASSADOR HOTEL
Atlantic City, New Jersey

JUNE 7 THROUGH 10, 1951

100th Annual Session, American Medical Association
ATLANTIC CITY, NEW JERSEY
JUNE 11 - 15, 1951

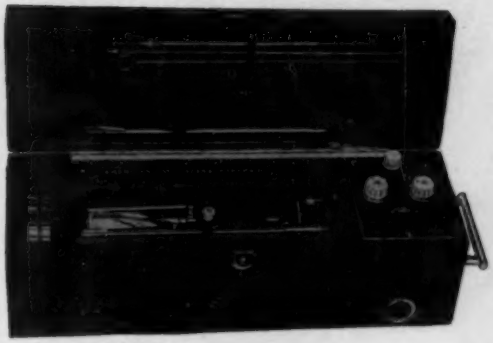
It is important to make hotel reservations at once for these meetings. Please address letters requesting reservations directly to the AMBASSADOR HOTEL, ATLANTIC CITY mentioning the meeting of the AMERICAN COLLEGE OF CHEST PHYSICIANS. Physicians planning to remain in Atlantic City for the meeting of the American Medical Association are required to place deposits with the Ambassador Hotel.

Write Today!

The usual excellent scientific program is being planned for the SEVENTEENTH ANNUAL MEETING OF THE COLLEGE

The Coryllos Thoracoscope

WITH SELF-CONTAINED CAUTERY AND LIGHT TRANSFORMER



600A as illustrated with footswitch and cautery-light transformer. The biopsy forceps illustrated in lid of case is an accessory instrument and is sold separately.

Biopsy Forceps, Cat. No. 389

A sturdy portable instrument for the double cannula pneumonolysis technique, which adequately meets the requirements of the American surgeon. The Coryllos Thoracoscope consists of telescope, two cannulae, light carrier, two extra lamps and sterilizable lighting cord. The long and short cautery electrodes are equipped with ventilating shields which permit air circulation in the pleural cavity. The self-contained cautery and light transformer obviates the necessity of purchasing relatively expensive high-frequency generators and transformers. The instrument is contained in a polished, substantial walnut case with carrying handle. A space is provided for the footswitch which is included.

Supplementary instruments such as curved electrodes, flexible cannula, transilluminator and aspirating tube, biopsy specimen forceps, infiltration needle, etc. are also available for those who desire a more elaborate armamentarium.

Consult your Dealer or Write to us for Literature

WAPPLER

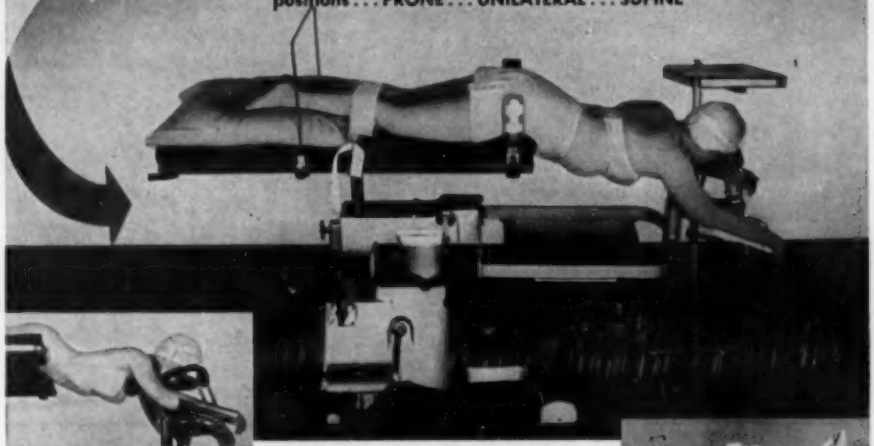
AMERICAN CYSTOSCOPE MAKERS, INC.

1241 LAFAYETTE AVENUE, NEW YORK 59, N. Y.

NOW! widely favored prone posture AVAILABLE TO ALL

The "American"
OVERHOLT-COMPER THORACIC TABLE

accommodates patient in all 3 primary positions . . . PRONE . . . UNILATERAL . . . SUPINE



Lateral Tilt Control renders sound lung uppermost. Both horizontal and vertical relationship of pectoral and pelvic girdles are crank controlled.

Entire abdomino-thoracic area in unobstructed suspension.

WRITE TODAY
for descriptive literature

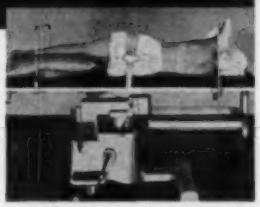
POSTURING ADVANTAGES

Pectoral Girdle is stabilized on especially designed adjustable Clavicular Supports without invading brachial plexus and axillary vessels.

Pelvic Girdle may be supported at symphysis and anterior superior spines.

Attainable range of thoracic cage and diaphragmatic excursion is greatly improved.

Facilitates posturing most favorable for natural drainage of bronchial secretions.



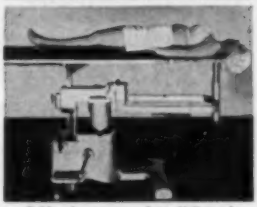


Table also accommodates Unilateral Position (top) and Supine Posture (bottom) for bronchoscopy with or without bilateral fluoroscopy.

AMERICAN STERILIZER COMPANY
Erie, Pennsylvania

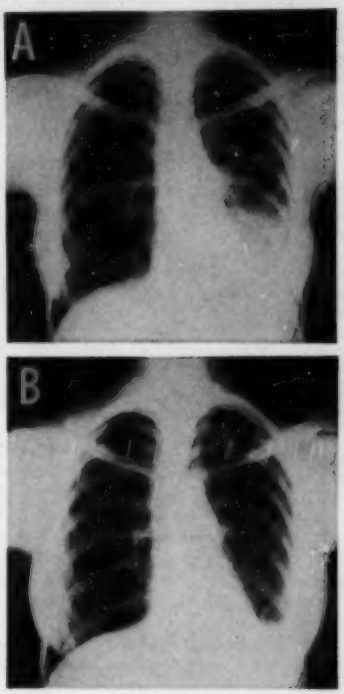
DESIGNERS AND MANUFACTURERS OF SURGICAL STERILIZERS, TABLES AND LIGHTS

Effective Chemotherapy in TUBERCULOSIS

DIHYDROSTREPTOMYCIN or Streptomycin, used alone or in combination with para-aminosalicylic acid, is recognized as a valuable and, in some instances, an essential adjuvant in the treatment of selected types and stages of tuberculosis.

Para-aminosalicylic acid is capable of inhibiting or significantly delaying the emergence of bacterial resistance to dihydrostreptomycin or streptomycin.

These drugs are not to be regarded as substitutes for traditional therapeutic methods. Rather, they serve best when properly integrated with bed rest and, where necessary, collapse measures or other forms of surgery.



A. Before Treatment
(9 days prior to Dihydrostreptomycin therapy) Diffuse lobular tuberculous pneumonia, lower half of left lung; thin-walled cavity above hilus (3 x 3.5 cm.).

B. After 3 Months' Treatment
(2 days after discontinuance of Dihydrostreptomycin) Considerable clearing of acute exudative process in the diseased lung; cavity smaller and wall thinner.

Detailed literature on the subject of chemotherapy in tuberculosis will be supplied upon request.

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

Merck Antituberculosis Agents

Streptomycin Calcium Chloride Complex Merck	Para-Aminosalicylic Acid Merck (PAS)	Crystalline Dihydrostreptomycin Sulfate Merck

The Council on Postgraduate Medical Education

The Pennsylvania Chapter

American College of Chest Physicians

AND

The Laennec Society of Philadelphia

A N N O U N C E

A Postgraduate Course in Diseases of the Chest

March 26 - 30, 1951

Warwick Hotel, Philadelphia, Pennsylvania

This course will emphasize the recent developments in all aspects of diagnosis and treatment of diseases of the chest. The course is open to all physicians, although the number of registrants will be limited. Applications will be accepted in the order in which they are received.

— TUITION FEE $50.00 —

AMERICAN COLLEGE OF CHEST PHYSICIANS
500 North Dearborn Street
Chicago 10, Illinois

I wish to apply for the course in Diseases of the Chest to be held in Philadelphia, March 26-30, 1951. Enclosed please find my remittance in the amount of $50.00 in payment of the tuition fee.

NAME .....

ADDRESS .....

CITY ..... STATE .....

Please make check payable to the American College of Chest Physicians.

3 IMPORTANT FORMS OF HEYDEN ORAL PENICILLIN

FINE HEYDEN CHEMICALS

Under your own label, you can now offer your customers 3 popular and highly effective ORAL forms of Heyden Penicillin, in a wide range of dosages to meet the exacting requirements of the medical and hospital fields.

SOLUBLE TABLETS: Crystalline Penicillin G Potassium (50,000 and 100,000 units, sealed in foil).

TROCHES: Crystalline Penicillin G Potassium (5,000 units, in silver foil; 10,000 units, in gold foil). Pleasantly flavored, slow to dissolve.

BUFFERED TABLETS: Crystalline Penicillin G Potassium (50,000, 100,000 and 250,000 units sealed in foil).

Remember!—when you standardize on Heyden antibiotics, both you and your trade are assured of superior quality, uniformity and potency—regardless of the form, dosages or quantity you purchase.

Other Heyden Penicillin and Streptomycin Products

PENICILLIN

Vials: Crystalline Penicillin G Potassium or Sodium; Crystalline Procaine Penicillin G in Sesame Oil with 2% Aluminum Monostearate w/v (cartridges, single- and multiple-dose vials) (also available in fortified form).

STREPTOMYCIN

Vials: Crystalline Dihydrostreptomycin Sulfate (1-gm. and 5-gm.).

Dihydrostreptomycin Sulfate (1-gm. and 5-gm.).

Streptomycin Sulfate (1-gm. and 5-gm.).

MANUFACTURER-DISTRIBUTORS

will be interested in Heyden's bulk service to packagers of penicillin and streptomycin. Cartons, unit containers, technical literature and package inserts, are available for your OWN personalized service. Write today for detailed particulars.

HEYDEN CHEMICAL CORPORATION

More and more every day

Every day more thousands upon thousands of *minographs** are made in TB case-finding surveys the world over. You see here some of the mobile Minograph clinics which have come off Picker drawing boards and out of Picker shops recently.

To entrust equipment of a chest survey program to Picker is to call upon a rich fund of practical experience in this exacting work. To entrust the fulfillment of *any* x-ray need to Picker is similarly satisfying.

*min'o-graph, mĭn'o-graph: a small photograph of a fluoroscopic image by means of the Picker Minograph x-ray apparatus.

Minobus Caravan in Belgian Congo

Minograph Trailer in Switzerland

U.S. Navy Ambulatory X-Ray Unit

Minobus Chest Clinic in Yugoslavia

U.S. Indian Service Minograph Transport

Connecticut Chest X-Ray Unit

U.S.P.H.S. Chest Survey Unit

Minograph Trailer in Portugal

Picker x-ray

PICKER X-RAY CORPORATION
300 FOURTH AVE., NEW YORK 10, N. Y.

DISEASES *of the* CHEST

VOLUME XIX FEBRUARY 1951 NUMBER 2

Surgical Repair of Mitral Insufficiency*

(A Preliminary Report)

CHARLES P. BAILEY, M.D., F.C.C.P.,
THOMAS J. E. O'NEILL, M.D., F.C.C.P.,
ROBERT P. GLOVER, M.D., F.C.C.P.,
WILLIAM L. JAMISON, M.D. and
HECTOR P. REDONDO RAMIREZ, M.D.†
Philadelphia, Pennsylvania

During the course of our surgical experiences with the relief of stenosis in mitral rheumatic disease we have been impressed by the fact that associated insufficiency of the mitral valve is a relatively uncommon occurrence, at least in significant form. Thus, in only about one half of the cases subjected to commissurotomy in our clinic has there been any associated regurgitation detectable by palpating the mitral valve orifice via the auricular appendage. Even the slightest regurgitant leak is discernible to the exploring finger as ventricular systole ejects the blood backward into the atrium at high velocity in the form of a jet. It would seem that as little as one or two cubic centimeters of regurgitant blood can be appreciated by such intracardiac palpation. Probably as much as 20 cc. of regurgitation per ventricular beat may be tolerated with relative impunity provided the heart can accommodate to this excess load gradually as is the case in naturally and slowly developing rheumatic valvular deformity.

However, there are cases of predominant mitral regurgitation in which no stenotic narrowing of the mitral orifice is detectable by palpation. Some of these persons appear to have what we have termed "paradoxical valvular dysfunction." In these the mitral valve feels large and normally flexible but appears to

*Read before the American College of Chest Physicians Ohio Chapter, Cleveland, Ohio, December 3, 1950.

†From the Department of Thoracic Surgery, and the Thoracic Surgical Research Laboratory of the Hahnemann Medical College and Hospital. Aided by the U. S. Public Health Grant H394, the Mary Bailey Research Foundation and the Deborah Research Society, Philadelphia, Pa.

Copyright, 1951, by the American College of Chest Physicians

open rather than to close upon ventricular systole. We assume that the chordae tendinae may be shortened or attached in such a way as to hold the valve orifice widely open at the time of ventricular systole. Valvular dysfunction might well be expected if the papillary system were distorted by disease in such a manner that its contraction could actively pull the valve leaflets open with each systole.

In addition to cases of relatively pure valvular dysfunction, there are a number of cases of mitral stenosis in which there is more than minimal or clinically insignificant associated mitral regurgitation. These cases have, in the past, been especially troublesome problems since commissurotomy employed to relieve mitral stenosis did not always improve the regurgitation and occasionally considerably exaggerated it.

The problem of correcting insufficiency of a valve is entirely different from that encountered in correcting stenosis since in the latter instance there is always sufficient valvular structure present, whereas in the former situation there may be relative lack of valvular tissue for one reason or another. Academically, although perhaps not practically at present, this deficiency might conceivably be overcome in one of several ways. Plastic prosthetic valves might be sutured within the mitral orifice. This method has been employed experimentally by Denton.[1] It is questionable whether such mechanical valves could be indefinitely tolerated within the human heart chambers, subject as they are to constant motion under high pressure variations. Accumulating experience with the insertion of foreign material anywhere in the body and especially within cardiac or vascular channels is not entirely reassuring in this respect.

Actual plastic procedures upon the heart valves employing the use of free tissue grafts to supplement the valvular deficiency would seem more reasonable. This, of course, would ideally require the circulation to be temporarily diverted through an artificial heart-lung apparatus so that a proper surgical exposure of the interior of the left ventricle could be obtained. Surgery of this magnitude must of necessity await the perfection of accurate and efficient heart-lung equipment for its satisfactory performance. It is quite possible that such an artificial heart-lung apparatus will be available for human use in the none too distant future. Indeed, there are already a number of investigators[2-9] who have devised equipment suitable for bypassing the heart and lungs as shown experimentally in animals.

Since 1940, we too, have been actively engaged in attempting to devise a practical (portable) apparatus capable of oxygenating and supporting the entire human circulation. Such equipment

would make possible many intracardiac operations and would also find a field of employment in many medical, pulmonary and cardiac conditions. With the combined efforts of the Drexel Institute of Technology, the Hahnemann Medical College, and the J. J. Ashton Company of New York, it has been possible to develop such an apparatus to a point where experimental animals have survived complete exclusion of all the blood entering the superior and inferior vena cava for periods up to 70 minutes (Fig. 1). This equipment is all contained within a portable unit which is approximately 30 by 18 by 15 inches (see Figs. 2a and 2b). The oxygen saturation of the blood which has passed through it is maintained at well over 90 per cent. There appears to be no serious hemolysis or other severe blood damage with our equipment. We have accomplished this by using standard industrial chemical and engineering know-know, a column of Stedman packing to oxygenate the blood, and a specially built flexiliner pump.[10]

Even with the aid of such an apparatus some question arises as to whether an intricate, freshly sutured repair or graft of the heart valve could withstand the constant movement and violent pressure changes to which these valves are normally subjected. At this stage in our development it would seem more reasonable to explore the more readily available methods of surgical relief at our disposal rather than to await with measured complacency the

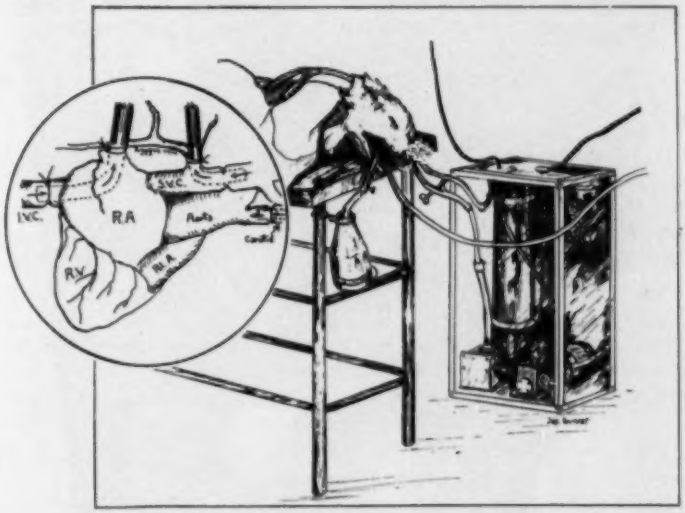


FIGURE 1: Heart-lung machine connected with experimental animal. Inset demonstrating cannulation of great vessels with exclusion of all systemic venous blood from the heart.

further development of such highly complex instruments and means.

In 1938, Murray[11] reported experiments with a small series of dogs in which he resected portions of the lateral mitral leaflet producing regurgitation. All dogs so treated promptly died. In another group of dogs he inserted an inverted vein graft completely through the left ventricle via a canulla, in an attempt

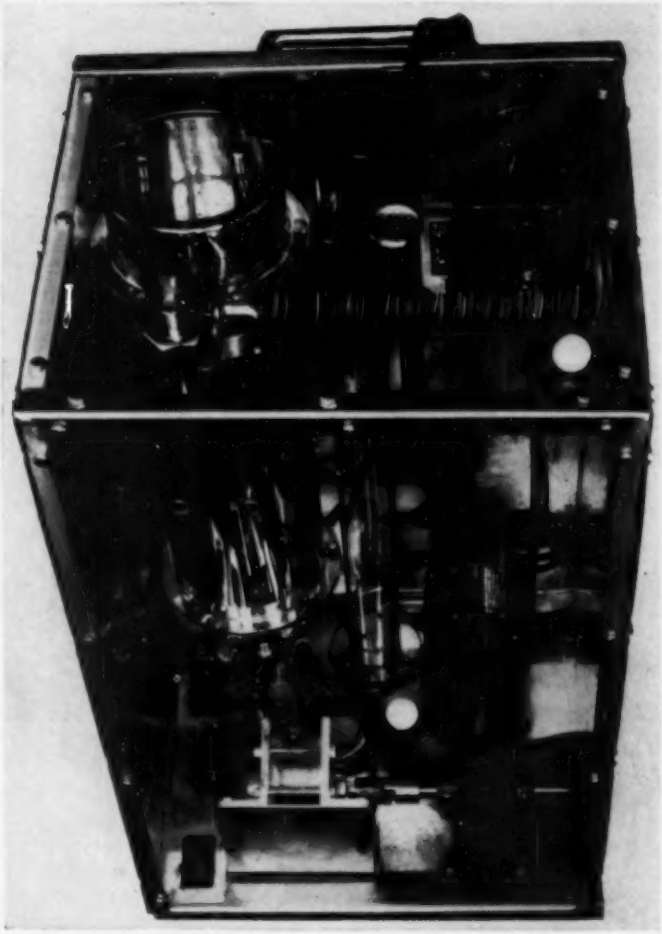


FIGURE 2a: Front view of heart-lung machine.

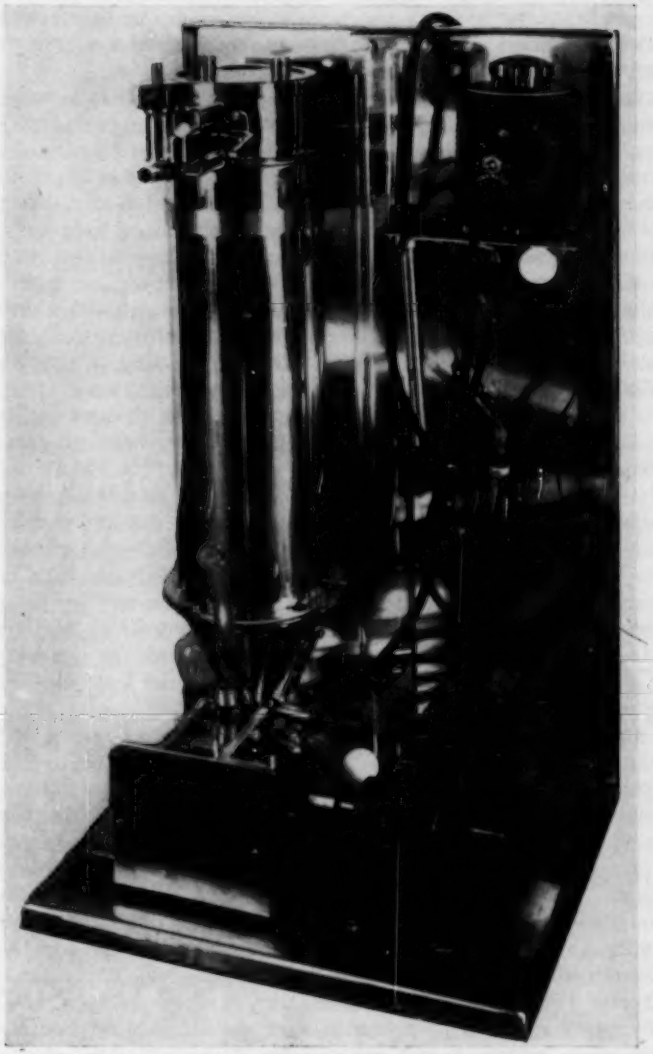


FIGURE 2b: More direct view of heart-lung machine.

to produce a flap or sling valve which would tamponade the mitral leak at each ventricular systole. While only two of eight dogs so treated actually survived, the duration of postoperative life was significantly longer than in the control series, and Murray felt that the regurgitation had been greatly reduced.

Murray's experiments were repeated in our laboratory with a somewhat modified technique and it soon became obvious that this principle was sound and that technical execution was not unduly difficult. However, in all instances, the free graft soon lost its resilience and became a shrunken fibrotic band. Obviously, its function as a flap valve was lost in the same degree. In a recent publication, Murray[12] has reported the application of this technique in human mitral stenosis. It seems probable that the immediate effect of the graft controls or diminishes the mitral regurgitation suddenly produced by resection of a portion of the mitral valve ring (as his technic calls for) and by so doing the otherwise anticipated immediately lethal result is avoided. In time, the gradual stiffening of the free graft with loss of valve function is accompanied by a gradual adjustment of the heart to the increasing regurgitation.

Certain disadvantages to the use of free vein grafts immediately present themselves. First and foremost among these is the rapid loss of efficiency of the valve flap due to atrophic changes. In the treatment of naturally occurring mitral insufficiency, a permanent type of control is mandatory. Secondly, the site of the donor graft is not within the confines of the operative field. This necessitates additional operative incisions to obtain femoral or internal jugular vein grafts together with sections of fascia lata or palmaris longus tendon.

For these and other reasons we considered other tissues which might prove suitable for intracardiac grafting. Templeton and Gibbon[13] in a series of animal experiments, sutured pieces of pericardial tissue as free grafts within the right auricle. While these grafts eventually became shrunken and fibrotic, they did not produce intracardiac thrombosis as might have been anticipated. Free grafts of pericardial tissue were therefore prepared and passed through the ventricles of mongrel dogs in a fashion similar to the one employed with the vein grafts. Again, the grafts functioned at first, but within a few weeks became shrunken and fibrotic. It soon became apparent that the use of free grafts of any tissue whatever, deprived as they are of their original blood and nerve supply is not suitable for long term application of flexible valvular tamponage.

These inadequacies suggested a third type of experiments employing a strip of pericardium as a pedicled graft or tube with

preservation of the normal nerve and blood supply at its base. Observations over a period of months indicated that these pedicled grafts functioned most adequately and showed no tendency to contract or become indurated. The method was therefore applied to clinical cases suffering from serious degrees of mitral regurgitation. All the previously established criteria for the selection of cases shown to be so satisfactory in our series of mitral commissurotomies for mitral stenosis were closely followed; i.e., single valve lesions, and the patient in a state of complete cardiac compensation prior to surgery. We have called the surgical procedure "Transventricular Pericardial Tamponage."

The suggested technic is as follows: The patient is postured in the true right lateral position. A long left lateral incision is made, running up posteriorly in the para-scapular line. The left 5th interspace is opened from the bodies of the vertebrae nearly to the internal mammary vessels. The lung is permitted to collapse and the pericardium is opened by an incision posterior and parallel to the left phrenic nerve.

A heavy silk suture on a curved atraumatic needle is used to place a purse-string about the base of the left auricular appendage. Sometimes two such purse-string ligatures are employed. A non-crushing (Satinsky) clamp is placed across the appendage somewhat distal to the sutures, and an incision is made into the tip of

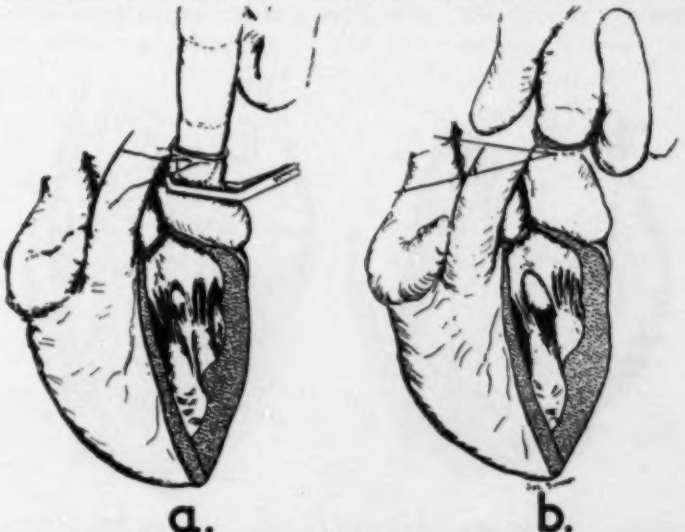


FIGURE 3: (a) Satinsky clamp occluding auricular appendage. A purse-string suture has been previously placed.—(b) Satinsky clamp is released. Finger inserted into auricular appendage. Purse-string tightened by assistant.

the appendage. This incision should ideally be just large enough to accommodate the right index finger, but if made too large can be reduced by the purse-string (Fig. 3a).

The index finger is inserted into the appendageal opening as the clamp is released. Long thumb forceps on either lip of the incised appendage steady it during this insertion. The finger is now in position to explore the interior of the left auricle (Fig. 3b). Exploration should include three definite objectives: (1) Determination of the integrity of the auricular septum and foramen ovale, (2) Localization (and counting) of the apertures of the pulmonary veins of both lungs, (3) Palpation of the mitral valve and estimation of the relative anatomical and physiological distortion. This latter includes an appreciation of the amount of existing regurgitation, presence or absence of stenosis, stiffness and character of the valve leaflets, size of the auriculo-ventricular aperture and localization of the point of regurgitation (if localized) in the length of the mitral slit.

After completing the exploration a decision is made as to the desirability of commissurotomy, and if appreciable stenosis is present, it is performed. After that, if not previously, the finger tip can be inserted with ease into the left ventricular chamber without completely blocking the flow of blood through the mitral orifice. The ventricular chamber may then be explored, and the fingertip through the mitral valve may be used to guide subse-

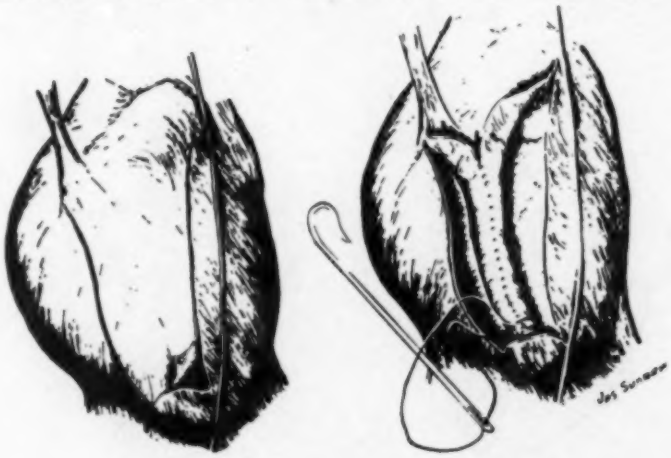


FIGURE 4: (a) Pedicled flap of pericardial tissue reflected anterior to phrenic nerve.—(b) Pedicled flap closed with suture to form a tube.

quent intracardiac maneuvers. We have called this technic, "transauricular intracardiac digital visualization."

The finger is now withdrawn from the heart and the appendage is gently clamped with a Satinsky clamp. The pericardium is incised just anterior to the left phrenic nerve, down to the diaphragm. Indeed, by pulling vigorously upon it, about one-half inch of the actual pericardial reflection upon the diaphragm may also be obtained. A parallel incision is made in the pericardium from 1½ to 2¼ inches medial to the former, also down to the diaphragm. By cutting it free from the diaphragm an adequately long, pericardial flap is obtained, pedicled at the cardiac base so that its nerve supply and most of the normal blood supply is retained (Fig. 4a). Any excessive pericardial fat is removed particularly toward the free end. Care must be taken to preserve the basal fat and any contained sizeable blood vessels. The flap is now folded longitudinally so that the smooth epicardial surface is exposed. Interrupted arterial silk sutures are employed to maintain this folding, thus converting the flap into a tube (Fig. 4b).

An ordinary surgical probe with a flat end containing an eye is bent into a smooth 15 degree arc. This eye is threaded with a strong heavy suture about 24 inches long and the free ends are then sewn through the very tip of the pedicled graft and tied so that each of them is independently secure in it.

The index finger of the right hand is again inserted into the left auricle and is passed through the mitral orifice into the

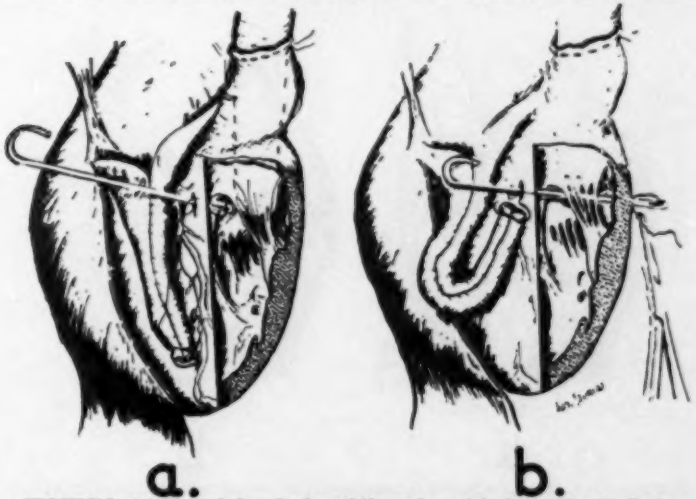


FIGURE 5: (a) Threaded probe forced through ventricular wall.—(b) Probe emerging lateral to posterior aspect of left ventricle.

ventricle. The upper or anterolateral commissure of the valve is thus located, and the epicardium of the ventricle over this point (or over the nearest avascular area to this point) is incised. The threaded probe, held in the left hand is now forced through the ventricular wall through this tiny incision, and becomes palpable to the intracardiac finger (Fig. 5a). It is thus guided in close proximity to the ventricular aspect of the mitral orifice down to the posterior commissure and into the mesh of chordae tendinae grouped at that point. The probe is now rotated so that it emerges slightly lateral to the posterior aspect of the left ventricle, care being taken to avoid coronary vessels in that area.

As soon as the eye of the probe emerges from the heart the suture becomes visible and is grasped by a hemostat in the hands of the assistant (see Fig. 5b). The probe is then drawn back and out of the heart (Fig. 6a). It will now be seen to be threaded upon only one of the two sutures running to the graft, and that one is cut thus detaching the probe from the graft-suture line. There is only minimal bleeding up to this point because of the small size of the puncture wounds in the heart. The posterior emerging suture is now pulled through the heart dragging the free end of the graft into the left ventricle and then out of it posteriorly (Fig. 6b). The graft tamponades the openings in the ventricular wall as it makes them, thus very little bleeding ensues. As soon as the graft is fully through the heart, and while still holding it on considerable tension, the basal portion is rapidly

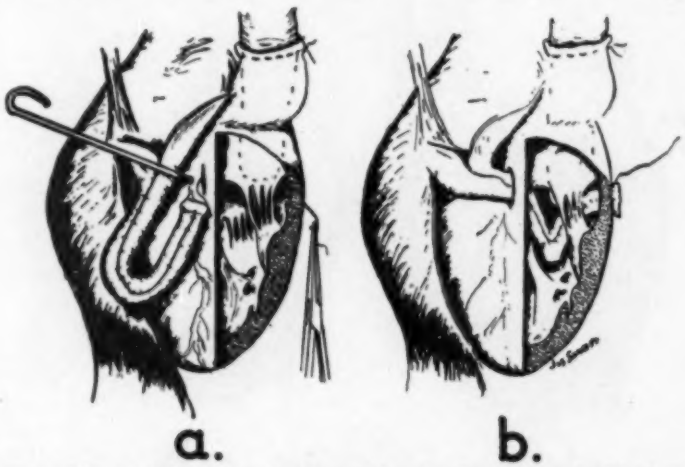


FIGURE 6: (a) Suture grasped by hemostat and probe withdrawn.—(b) Emerging suture has been pulled through the heart dragging the free end of the graft into the left ventricle and out of it posteriorly.

sutured to the epicardium of the ventricle. Tension on the free end of the graft is released allowing it to partially retract into the ventricle. When just the tip remains out of the heart it is secured to the epicardium by suture. If it does not promptly retract into the ventricle to afford needed slack for valvular action, the intracardiac finger may push upon the pericardial sling to force it to pull back into the heart. Within a few minutes the tonus of the ventricular musculature grips and holds the end of the graft securely.

The intracardiac finger can now appreciate the movement of the graft and its valvular action. A graft of suitable size, properly placed, and with adequate redundancy will completely tamponade and prevent the previously recognized regurgitation (Figs. 7a and 7b). The intracardiac finger can readily evaluate the efficiency of the new valvular system, and the clinical response can be prognosticated with reasonable accuracy.

Objections that the graft may not function well are based, first, upon lack of confidence in the technical ability of the operator to carry out the previously described procedure and, second, upon fears for the eventual fate of the graft. The former question may be resolved by increasing experience among surgeons. The latter is that in time the graft may deteriorate, become rigid and functionless, thus returning the mechanical burden of regurgitation to the unprotected heart. This question can not be completely

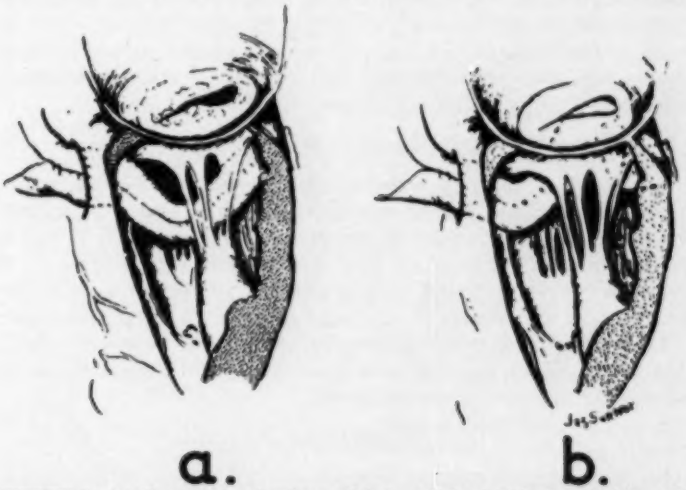


FIGURE 7: (a) Conception of valve pedicled graft in ventricular diastole.—(b) Conception of valve pedicled graft in ventricular systole blocking mitral orifice in preventing regurgitation.

resolved until the passage of time reveals the true condition. However, since the natural blood and nerve supply of the pericardial graft is largely maintained, it is presumed that it will retain its elasticity and flexibility indefinitely. Indeed, such pedicled grafts of pericardium, mobilized and then sewn to some extracardiac tissues do maintain these qualities indefinitely. Unless the operative mortality should prove higher than we now believe probable in the light of our small series of grafted cases, coupled with our experiences embracing 111 commissurotomy operations for mitral stenosis,[14] it would seem that the use of this procedure is entirely justified and should greatly relieve the patients so treated. The mechanical rest afforded to the myocardium would probably prolong life to a considerable degree, since the graft, even if it did eventually become functionless, would in no way subsequently impair cardiac action.

To date we have operated upon seven cass of mitral regurgitation by this technic. Two of these were cases of mixed mitral stenosis and insufficiency, and commissurotomy was performed to relieve this stenosis as the first step in the combined operative procedure. Of them six were considered successful in that the regurgitant leak palpable by the intracardiac finger was diminished by at least 75 per cent. In three cases the leak was considered to be completely controlled. In the remaining one there was little or no control of the regurgitation as measured by the palpating finger. We believe that in this instance the graft was improperly placed. We now consider it essential that the graft lie close to the valve orifice, must be reasonably lax, and preferably should run accurately through the network of chordae tendinae grouped at either extremity of the mitral slit.

SUMMARY AND CONCLUSION

A method of applying a pedicled pericardial graft under direct intracardiac digital control has been developed which is immediately effective in controlling serious mitral regurgitation of either pathological or surgical (during commissurotomy) origin. It is hoped and presumed that such grafts will prove permanently effective. Only the passage of time can finally prove this presumption.

In seven human cases so treated there have been no deaths. One of the cases was not considered successful probably due to inaccurate positioning of the graft.

RESUMEN

Se ha creado un método para aplicar un injerto de pericardio pediculado bajo control digital intracardiaco, el cual es inmediatamente efectivo para controlar la seria regurgitación mitral, ya

se trate de la de origen patológico o de origen quirúrgico (durante comisurotomía).

Se presume y se espera que tales injertos sean después de efectividad permanente. Solo el tiempo puede decir si esto es cierto.

En siete casos humanos tratados no ha habido defunciones. Uno de los casos se consideró como ineficazmente resuelto probablemente debido a una posición inadecuada del injerto.

RESUME

Les auteurs ont réalisé une technique qui permet le traitement de l'insuffisance mitrale. Ils utilisent dans ce but une greffe péricardique pédiculée, sous contrôle du doigt introduit directement dans les cavités cardiaques. Ils espèrent que de telles greffes pourront avoir un effet permanent. Seule l'observation prolongée pourra en donner la preuve. Dans 7 cas traités par leur méthode, il n'y a eu aucun décès. Un seul cas ne fut pas suivi de résultats immédiats, probablement a cause d'une position défectueuse de la greffe.

REFERENCES

1 Denton, G. R.: "A Plastic Prosthesis (Without Moving Parts) For the Atrio-Ventricular Valve," Read at Clinical Session of the American College of Surgeons, October 23, 1950.
2 Stokes, Thomas Lane and Gibbon, John H., Jr.: "Experimental Maintenance of Life by a Mechanical Heart and Lung During Occlusion of the Venae Followed by Survival," *Surg., Gyn. and Obst.*, 91:138, 1950.
3 Jongbloed, J.: "The Mechnical Heart-Lung System," *Surg., Gyn. and Obst.*, 89:684, 1950.
4 Sewell, William H., Jr. and Glenn, William L.: "Experimental Cardiac Surgery," *Surgery*, 28:474, 1950.
5 Sirak, Howard D., Ellison, Edwin H. and Zollinger, Robert M.: "Cardiotomy into Empty Left Ventricle Surgery," *Surgery*, 28:225, 1950.
6 Leed, Sanford E., Gray, Norma N. and Cook, Orrin S.: "Prolongation of Acclusion of Cava in Dogs by Diversion of the Circulation," *Surg., Gyn. and Obst.*, 91:399, 1950.
7 Welch, C. S., Wesolowski, S. A., Miller, H. H. and Halkett, J. A. E.: "Replacement of the Heart by a Mechanical Extra-corporeal Pump," *Bull. New England Med. Center*, 12:41, 1950.
8 Bjork, V. O.: "Brain Perfusions in Dogs with Artificially Oxygenated Blood," *Act. Chir. Scand.*, 1948, 96: Suppl. 137 (Lund).
9 Dennis, C.: "Artificial Maintenance of the Circulation," Read at a Symposium on Cardiovascular Research, U. S. Public Health Service, Washington, 1950.
10 Fink, C. E., Rehmus, Frederick, H., Ramirez, H. P. R. and Jamison, William L.: "Development and Use of the Drexel-Hahnemann-Vanton Heart-Lung Machine," To be published.
11 Murray, Gordon, Wilkinson, F. R. and McKenzie, R.: "Reconstruction of the Valves of the Heart," *Canada M. A. J.*, 38:317, 1938.
12 Murray, Gordon: "Treatment of Mitral Valve Stenosis by Resection and Replacement of Valve Under Direct Vision," *Archives of Surgery*, 61:903, 1950.
13 Templeton, John Y., III and Gibbon, John H., Jr.: "Experimental Reconstruction of Cardiac Valves by Venous and Pericardial Grafts," *Ann. Surg.*, 139:161, 1949.
14 Bailey, C. P., Glover, R. P. and O'Neill, T. J. E.: "The Surgery of Mitral Stenosis," *Jour. Thoracic Surg.*, 19:16, 1950.

Serum Concentrations of Para-Aminosalicylic Acid (PAS) Produced by Various Forms of PAS*

DOUGLAS K. DUNCAN, M.D.,
Fellow in Surgery, Mayo, Foundation, Rochester, Minnesota,
DAVID T. CARR, M.D.,
Division of Medicine, Mayo Clinic, Rochester, Minnesota,
KARL H. PFUETZE, M.D., F.C.C.P.,
Mineral Springs Sanatorium, Cannon Falls, Minnesota,
MARSCHELLE H. POWER, Ph.D.,
Division of Biochemistry, Mayo Foundation, Rochester, Minnesota.

Para-aminosalicylic acid (PAS) is now generally accepted as an effective antibacterial agent in the treatment of certain forms of tuberculosis when administered alone or in combination with one of the streptomycins. However, there remains a great deal of uncertainty as to the best method of administering the drug. Both the free acid and the sodium salt of PAS have been given in various dosage forms in an effort to diminish the symptoms of gastro-intestinal irritation which the drug produces. We have given the free acid as compressed uncoated tablets, enteric-coated tablets, enteric-coated granules, capsules, and as powder mixed with food or suspended in a liquid such as milk. The sodium salt has been given as a solution in water mixed with various fruit juices. Although an occasional patient preferred one of the forms of the free acid, most patients have been able to take larger daily doses of PAS as a solution of the sodium salt. This is in agreement with the reports of most clinical investigators.

However, it is obvious that the total daily dose is of less importance than the concentration of PAS that is present in the blood serum after administration of each of these forms of the drug. In 1949 Lehmann[1] advised against the use of the sodium salt of PAS stating, "We have generally used the PAS acid in the granules and not the sodium salt. The reason for not using the sodium salt is that it is very soluble in water, rapidly absorbed in the intestinal canal, and rapidly excreted by the kidneys. The blood level will therefore not be as high as one might except from the relatively large dose. The PAS acid is only soluble in 0.4 per cent in water and is not absorbed in the intestinal canal before neutralization by the intestinal juice." More recently he[2] has written, "Whether PAS should be used routinely as an acid enteric coated

*Abridgment of thesis submitted by Dr. Duncan to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

granule, or as the sodium salt is still a question to be answered."

A review of the literature has revealed a paucity of data on the concentrations of PAS in the blood serum of patients following the administration of various forms of the drug. Soderhjelm[3] determined the concentration of PAS in the blood serum of four children following administration of free acid PAS and its sodium salt. Twenty minutes after the oral administration of 0.05 gm. of free acid PAS per kilogram of body weight, the concentration of free PAS in the blood serum was between 6 and 12 mg. per 100 cc. Corresponding doses of sodium PAS resulted in comparable concentrations in the serum. Shamaskin[4] also has compared the concentration of PAS in the blood serum of 10 patients following the administration of comparable doses of free acid PAS in the form of powder and enteric-coated capsules, and sodium PAS in solution. He found that the free acid powder and the solution of the sodium salt gave similar concentrations with higher peaks than those obtained following the administration of comparable doses of enteric-coated capsules. However, a "therapeutic concentration" was maintained over a longer period of time when the capsules were given.

Owing to our uncertainty as to which form of PAS resulted in the greatest concentration of PAS in the blood serum the following investigation was carried out: Six patients with various manifestations of tuberculosis but without evidence of renal disease were selected. During successive weeks, after a period of 36 hours in which no PAS was administered, a single dose of 3 gm. of PAS or its equivalent was given orally in the following forms: compressed tablets of the free acid, enteric-coated granules of the free acid which contained 70 per cent PAS by weight, the free acid powder, and a solution of the sodium salt of PAS.* The free acid powder was given during two successive weeks, first with sufficient sodium bicarbonate to alkalinize the urine, and second with enough ammonium chloride to acidify the urine. Specimens of blood were drawn 1.5, 3.0, 4.5, and 6.0 hours after the administration of the single dose and the amounts of free† and total PAS in the blood serum was determined by a modification of the technic of Klyne and Newhouse.[5] The urine was collected for 24 hours following the administration of the dose of PAS and the amount of free and total PAS in the specimen was determined

*The PAS used in this study was supplied by Parke, Davis & Company, Detroit, Michigan, Merck & Co., Inc., Rahway, New Jersey, and Herts Pharmaceuticals Ltd., Welwyn Garden City, England.

†The term "free PAS" is used in this paper with the knowledge that the concentration of para-aminosalicylic acid plus para-aminosalicyluric acid is being measured. The exact proportion of these two compounds in the blood and urine is not known.

by the same method. After the data from this small group of patients had been analyzed, a group of 20 patients was studied in less detail. The free PAS in the blood serum was determined 1.5 hours after a single dose of 3 gm. of free acid PAS powder and 1.5 hours after a single equivalent dose (4.1 gm.) of the sodium salt of PAS had been administered. The free PAS in the blood serum was also determined 1.5 hours after the last of five doses of 3 gm. of free acid PAS given in the form of compressed tablets at intervals of three hours. The same measurement was made following the same dose of free acid PAS powder and a comparable dose of the sodium salt of PAS. These studies were made at weekly intervals and no PAS was given for 36 hours preceding each study.

Results

The average concentrations of both free and total PAS in the blood serum of the six patients receiving all five dosage forms of PAS are recorded in table I. The data reveal that most of the PAS in the blood serum at any time was in the form of free PAS. The peak concentration was greatest after the administration of the sodium salt of PAS and least after administration of compressed tablets of the free acid. However, the greatest concentration following the administration of the sodium salt of PAS was found in the 1.5 hour specimen, the concentration falling sharply throughout the six hours of observation. In contrast, when compressed tablets of PAS were given, the greatest concentration was found in the latter half of the six hours of observation. The concentrations following the administration of the free acid PAS powder were not affected by the acidification or alkalinization of the urine and were comparable to, though lower than, the concentrations obtained when the sodium salt of PAS was given.

TABLE I

Average Concentration of PAS in the Blood Serum of Six Patients (mg. per 100 cc.) After a Single Dose of 3 gm.

Hours after administration	PAS Tablets		PAS enteric-coated granules		PAS powder with $NaH\ CO_3$		PAS powder with NH_4Cl		Sodium PAS Solution	
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
1.5	1.2	1.5	3.3	3.3	5.1	5.7	4.9	5.6	8.9	9.4
3.0	2.4	2.8	2.9	3.7	2.6	3.8	4.4	5.2	5.2	5.3
4.5	2.9	3.6	4.1	5.1	1.4	2.1	2.5	3.4	2.5	3.3
6.0	2.8	3.4	3.1	4.0	0.7	1.1	1.2	2.3	1.1	1.9

Following administration of enteric-coated granules of free acid PAS, the peak concentration was less than when the sodium salt of PAS or the free acid powder was given but greater than that following administration of the compressed tablets. However, the concentration was maintained at approximately the same level throughout the six hours of observation.

The concentrations of free PAS in the blood serum of the group of 20 patients are recorded in table II. The average concentrations 1.5 hours after single doses of free acid powder and the sodium salt of PAS were more nearly the same in this larger group. Of more importance was the concentration of free PAS in the blood

TABLE II

Concentration of Free PAS in Blood Serum

	1.5 HR. AFTER SINGLE DOSE*		1.5 HR. AFTER FIFTH DOSE* AT 3 HR. INTERVALS		
Patient	PAS powder	Sodium PAS	PAS tablets	PAS powder	Sodium PAS
1	7.3	8.1	6.6	17.4	14.6
2	7.3	6.4	6.0	12.0	11.0
3	7.7	8.5	5.6	14.4	11.8
4	4.2	4.8	13.4	20.0	15.0
5	2.7	5.8	7.0	19.4	25.4
6	4.0	5.8	11.4	21.0	12.8
7	5.8	8.3	10.4	15.6	11.4
8	7.3	9.0	10.0	14.4	16.4
9	6.9	6.7	8.4	15.6	19.4
10	7.4	11.1	1.8	14.0	15.6
11	8.2	10.6	9.2	11.0	8.6
12	6.5	5.7	1.8	9.0	10.8
13	5.5	5.4	1.2	7.0	8.2
14	3.2	6.4	6.2	12.8	12.8
15	5.6	4.0	8.0	10.6	13.2
16	5.2	5.8	23.4	21.4	25.6
17	4.6	5.9	13.8	16.2	17.0
18	5.2	6.9	8.4	16.2	17.2
19	4.2	7.1	12.6	18.6	14.0
20	4.0	5.9	18.2	14.0	17.2
Mean	5.6±0.35	6.9±0.41	9.2±1.19	15.0±0.88	14.9±0.88

*3 gm. of PAS or equivalent.

serum 1.5 hours after the last of five doses of the various forms of PAS given at intervals of three hours. The average concentration was approximately the same following the administration of the free acid powder and the sodium salt of PAS. However, when compressed tablets of free acid PAS were given the average concentration 1.5 hours after the fifth dose was significantly lower.

It will be noted that the patients who had low concentrations following administration of one form of the drug tended to have low concentrations in all of the studies and those with high concentrations in one of the tests were high in all of them. It will also be seen that the concentration varied more from patient to patient when the compressed tablets of free acid PAS were given. These same variations were also true of the six patients in the more detailed study.

The average amounts of free and total PAS in the 24-hour collections of urine from these six patients are given in table III. These have been calculated as percentages of the dose of PAS. The unusually large amount that was recovered when enteric-coated granules of the free acid were given suggests that more than the calculated dose of 3 gm. of PAS was administered by this method. The rest of the data indicate that most of the drug was absorbed and excreted in the urine within 24 hours, regardless of the method of administration.

Comment

The results of these studies indicate that comparable peak concentrations of PAS were present in the blood serum following the administration of either the sodium salt of PAS or the free acid itself provided the free acid was in a readily available form such as a powder. Administration of the compressed tablets of enteric-

TABLE III

Average Free and Total PAS in 24-Hour Specimens of Urine Following a Single Dose of 3 gm.

	PAS IN URINE*	
	Free	Total
PAS tablets	19.3	75.8
PAS enteric-coated granules	45.4	123.1
PAS powder with sodium bicarbonate	32.6	68.1
PAS powder with ammonium chloride	23.8	64.6
Sodium PAS solution	43.3	81.8

*Percentage of the dose.

coated granules of free acid PAS resulted in significantly lower peak concentrations of PAS in the blood serum. This was probably due to the fact that the tablets as well as the enteric-coated granules disintegrated slowly. In vitro studies with the tablets revealed that they broke up very slowly whether placed in water or in a solution of sodium bicarbonate. However, administration of the compressed tablets or enteric-coated granules of free acid PAS resulted in greater concentrations of PAS in the blood serum six hours after a single dose than when sodium PAS or the free acid powder was given. Whether this retardation of absorption is of any clinical value is not yet known. The available evidence suggests that it is not necessary to maintain a therapeutically effective concentration of PAS in the blood serum 24 hours a day. Feldman and his associates[6] have reported that a single parenteral injection of a solution of sodium PAS once each day was effective in controlling experimental tuberculosis in guinea pigs, and Bogen and his co-workers[7] stated that 2 gm. of PAS given orally three times each week was markedly effective in the experimental treatment of tuberculous guinea pigs.

As mentioned before, most patients have been able to take a larger daily dose of PAS in the form of the sodium salt than when any of the other preparations was given. The results of our studies indicate that the sodium salt of PAS is a satisfactory form of the drug and that it can be administered with confidence that an effective concentration will be produced in the blood serum.

SUMMARY AND CONCLUSIONS

The concentration of free and total PAS in the blood serum of 26 patients was determined after single and multiple oral doses of various forms of free acid PAS and the sodium salt of PAS.

Free acid PAS powder and the sodium salt of PAS yielded approximately the same concentrations after single or multiple oral doses. Compressed tablets or enteric-coated granules of free acid PAS gave lower concentrations than either of the first two, apparently due to delayed rather than incomplete absorption of the drug.

The concentration was not affected by the concurrent administration of sodium bicarbonate or ammonium chloride.

As sodium PAS causes fewer symptoms of gastro-intestinal irritation, it is the preparation of choice for most patients.

RESUMEN Y CONCLUSIONES

Se determinó la concentración del PAS libre y total en el suero sanguíneo de 26 pacientes después de dosis orales únicas y múltiples de varias formas del ácido libre y de la sal sódica del PAS.

El polvo del ácido libre y la sal sódica del PAS dieron aproximadamente las mismas concentraciones después de dosis orales únicas o múltiples. Las tabletas comprimidas o los gránulos de revestimiento entérico del ácido libre del PAS dieron concentraciones más bajas debido, aparentemente, más bien a la absorción demorada que a la absorción incompleta de la droga.

No afectó la concentración la administración concomitante de dicarbonato de sodio o cloruro de amonio.

La sal sódica del PAS es la preparación de elección para la mayoría de los pacientes, pues causa menos síntomas de irritación gastrointestinal.

REFERENCES

1 Lehmann, J.: "The Treatment of Pulmonary Tuberculosis With PAS," In Veterans Administration: *Minutes; Seventh Streptomycin Conference*, Washington, D. C., Veterans Administration Area Office, 1949, pp. 293-300.
2 Lehmann, Jorgen: "The Treatment of Tuberculosis in Sweden with Para-aminosalicylic Acid (PAS): A Review," *Dis. of Chest*, 16:684, 1949.
3 Soderhjelm, Lars: "Serum Para-aminosalicylic Acid (PAS) Following Oral Ingestion in Children," *Texas Rep. Biol. and Med.*, 7:471, 1949.
4 Shamaskin, A.: "Rate of Absorption and Toxicity of Paraminosalicylic Acid. A Comparative Study of Enteric Coated Capsules, Powder, and a Solution of Sodium PAS: Preliminary Report," In Veterans Administration: *Minutes; Eighth Streptomycin Conference*, Washington, D. C., Veterans Administration Area Office, 1949, pp. 126-230.
5 Klyne, W. and Newhouse, J. P.: "Determination of p-Aminosalicylic Acid in Body Fluids," *Biochem. J.*, 44:vii, 1949.
6 Feldman, W. H., Karlson, A. G., Carr, D. T. and Hinshaw, H. C.: "Parenteral Administration of P-aminosalicylic Acid (PAS) in Experimental Tuberculosis," *Proc. Staff Meet., Mayo Clinic*, 24:220, 1949.
7 Bogen, Emil, Loomis, R. N. and Drake, W. W.: "Para-aminosalicylic Acid Treatment of Tuberculosis: A Review," *Am. Rev. Tuberc.*, 61:226, 1950.

Pathology of Tuberculosis Treated with Streptomycin: A Review of 34 Cases*

OSCAR AUERBACH, M.D., F.C.C.P., LEO WEISS, M.D. and GRANT N. STEMMERMANN, M.D.
Staten Island, New York

In a previous report of a small series of cases of tuberculosis treated by streptomycin, we observed a number of anatomic changes which seemed directly attributable to the effects of streptomycin. The present study is based on 34 cases which received streptomycin therapy for variable periods during their stay in the hospital. Since this is an autopsy series the findings are necessarily weighted in favor of unsuccessful therapeutic results. An attempt will be made to evaluate cases in which the infecting organisms were still sensitive to streptomycin at death, those in which resistance had developed, and those in which chemotherapy had not been pursued for some time prior to death although the organisms were still sensitive. We shall also attempt to stress the difficulties encountered in such a study.

Review of Literature: Baggenstoss, Feldman and Hinshaw[1] reported the first pathological studies of streptomycin-treated cases in human tuberculosis. Among five cases of miliary tuberculosis, they noted, in the four receiving prolonged therapy, histopathological evidence of an inhibitory action exerted by streptomycin. This evidence consisted of regression and healing of miliary tubercles. Their criteria of healing were fibrosis, hyalinization and absence of caseation in miliary tubercles. They felt that the healing was atypical in that there was a diffuse, even fibrosis of the entire lesion rather than the usual encapsulation. They noted considerable variation in healing of different organs. The important factors for these variations were felt to be: 1) mechanical factors such as location of organ, blood and lymph circulation, and anatomicohistological structure, 2) inherent differences in native resistance of different organs as pointed out by Rich,[2] 3) size and mass of lesion, and 4) concentration of streptomycin in fluids and tissues. In this paper no note of changes in streptomycin sensitivity was made.

---

*From the Laboratory Service, Halloran Veterans Administration Hospital, Staten Island, New York.

Sponsored by the Veterans Administration and published with approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Kidd,[3] in a short paper, reported on the modification of tuberculous lesions in seven cases of miliary tuberculosis and the findings were later elaborated by Flory, et al.[4] In general, their findings coincided with those of Baggenstoss, Feldman and Hinshaw.[1] They described a number of modifications of miliary tubercles. One type consisted of small loose, fibrotic scars believed to represent completely healed miliary tubercles. Another type consisted of "soft" tubercles with scars at one border. A third type ("ring" tubercles) consisted of large (3 mm.) miliary tubercles showing central necrosis, surrounded by an incomplete ring of collagen and beyond, another zone of necrosis. The necrotic areas contained numerous acid-fast bacteria. This type of tubercle was found in cases relapsing after clinical remission. They interpreted these as indicating that with the advent of streptomycin-resistant organisms, the infection spread outwards from the unhealed caseous centers through the fibrous wall and enveloped the original tubercle. As far as we can determine from their descriptions and photograph (Fig. 13, Flory, et al) they appear to be describing a reappearance of perifocal reaction. Three of their cases (3, 6 and 7) had pulmonary tuberculosis with cavitation. They noted no changes in the walls of these cavities. These same cases and case 4 with a retro-pharyngeal abscess had intestinal tuberculosis, but no correlation is made by the authors between the opportunity of spread via the gastro-intestinal tract lumen and the presence of the intestinal tuberculosis. They did point out a relationship between the morphologic findings indicative of activity of disease and the appearance of streptomycin-resistant tubercle bacilli.

Auerbach and Stemmermann[5] in a previous report described seven autopsy cases of tuberculosis. They stressed the importance of knowledge of the streptomycin-sensitivity of the tubercle bacilli and of a large background of personal experience with human tuberculosis so that individual streptomycin-treated cases could be compared with similar non-treated cases of comparable age, race and duration. Their most striking morphologic finding was the rapid and extensive resolution of the perifocal reaction surrounding tuberculous foci with consequent diminution of the ultimate amount of fibrosis. Pulmonary cavities were shown to present more evidence of healing than expected in comparable cases. The tuberculous foci on superficial surfaces (laryngo-bronchial tree, intestine, lungs, meninges, pleura, etc.) showed more healing than lesions of solid organs. No evidence that streptomycin prevented dissemination of tubercle bacilli by either the bronchial or lymphohematogenous routes was found but there was more rapid healing of the disseminations.

Silverthorne and Silverman[6] studied 20 cases of streptomycin

treated tuberculosis. Three were progressive primary disease of children, six were hematogenous tuberculosis in adults and 11 chronic pulmonary disease. They felt that no single gross or histologic change could be solely ascribed to streptomycin therapy as all changes noted could also be found in 20 similar untreated cases that were used as controls. The "ring" lesions of Flory, et al, were not found. In some cases, they were impressed by absence of perifocal reaction but stated it was not a ubiquitous finding. They report no data on streptomycin-sensitivity of organisms to correlate with the presence or absence of perifocal reaction. They felt that cavity walls showed no demonstrable effect.

Mahon[7] reported on 56 autopsied cases and 55 surgical pulmonary specimens of streptomycin-treated tuberculosis. This is the most extensive study to date. He also recognized that there are no specific pathologic changes peculiar to tuberculous lesions treated by streptomycin. The healing changes induced by streptomycin did not differ from those of natural healing processes. Nevertheless, he felt that the time for healing to occur was shortened by the ability of streptomycin to inhibit the multiplication of tubercle bacilli. He recognized the clearing of perifocal reactions, the greater healing in thin-walled cavities as demonstrated by healthy granulation tissue linings, decreased active endobronchial tuberculosis and the greater healing of miliary foci in the lungs than in solid organs. He felt the effects in chronic fibrocaseous and fibrocavernous tuberculosis were indefinite. He realized that continuation of streptomycin therapy after demonstration of in vitro insensitivity of the tubercle bacilli had no effect on the course of disease.

Material: Chronic pulmonary tuberculosis was present in 33 of our 34 cases. The therapy was directed to the pulmonary disease in all but three in which the accompanying meningitis was the disease treated and in one case in which an epididymitis was treated. Tuberculous meningitis was the sole disease in one patient.

Dosage: In one instance the total dosage was 21 grams. In all others it varied from 42 grams to more than 300 grams. Some of the cases receiving larger dosages had treatment over a period lasting from one to more than two years.

Sensitivity Studies: Evaluation of this all important factor is beset with great difficulties. However, a good correlation between clinical and anatomic findings is extremely difficult unless this factor is considered. The following are some of the problems which we encountered: 1) The source of tubercle bacilli may be cut off before sensitivity studies are completed. This occurs in cases of chronic pulmonary tuberculosis in which the cavities close or are removed by excision therapy. In cases of meningitis block of the spinal canal or disappearance of the bacilli from the spinal fluid

TABLE I: Tubercle Bacilli Sensitive—At or Near Time of Death.

	Case No.	Age	Color	Duration of Pul. Tuberculosis in Months	Days of Known Insensitivity	Last Dose; Days Prior to Death	Days Since Last Known Sensitivity	Total Grams of Streptomycin
1.	A-7-48	48	C	13	0	0	0	133
2.	A-199-48	42	C	..	0	0	0	70
3.	A-26-47	52	W	17*	No data	32	15	104
4.	A-142-49	47	W	6	No data	0	47	78***
5.	A-51-49	56	W	18	No data	52	63	67
6.	A-10-50	33	W	39	No data	1	67	173
7.	A-9-48*	21	C	23	No data	0	97	163

	Case No.	Tracheo-bronchial Tree	Larynx	G. I. Tract	Miliary Foci	Perifocal Reaction	Cavity	Extrapulmonary Tuberculosis
1.	A-7-48	0	0	0	Spleen	+	Increased collagen.	0
2.	A-199-48	0	0	0	0	Not applicable.	Not applicable.	Subperiosteal abscess right 6th and 7th ribs; tuberculoma; meningitis.
3.	A-26-47	0	0	0	Lung, liver, spleen, kidney.	0	Inspissated.	Third and fourth lumbar vertebrae; multiple tuberculomata cerebrum, cerebellum. Meningitis; prostate.
4.	A-142-49	0	0	0	Spleen, liver, adrenal.	+	Healing.	Pleura.
5.	A-51-49	Trachea, left main bronchus (healing).	+	0	0	±	Hyalinization.	0
6.	A-10-50	0	0	0	Spleen, liver, adrenal, kidney.	+	Healing.	Empyema with squamous epithelialization. Pulmonary artery perforation.
7.	A-9-48**	0	0	0	0	0	Increased collagen.	0

*Duration of miliary tuberculosis. **Post-pneumonectomy operative death. ***Received para-aminosalicylic acid.

may make further study impossible. 2) Attempts to culture acid-fast bacilli may be unsuccessful. Since growth takes a number of weeks, a patient may die before it is realized that the attempt was unsuccessful. To prevent this loss we have made it a routine to do sensitivity studies on material from active tuberculous lesions in all autopsy cases that have been under treatment with streptomycin.

Results of Sensitivity Tests: Our cases fall into three groups: 1) Those in which the tubercle bacilli were sensitive to streptomycin at or near the time of death, 2) those in which streptomycin resistance developed during or after a course of treatment or who had not been under treatment for a considerable period of time. 3) Those in which the sensitivity of the infecting organism was not known at the time of death. Among these are included persons in whom sensitivity studies were performed too long before death to give any indication of the status of the tubercle bacilli at death.

1. *Cases in Which the Organisms were Sensitive to Streptomycin (Table 1):* There are seven cases which fall into this category. Three were known to be sensitive within 15 days of death; the other four were sensitive 47 to 97 days before death. These showed the beneficial changes attributable to streptomycin therapy, namely: 1) a slight or absent perifocal reaction about pulmonary tuberculous lesions, 2) increased hyalinization in the walls of pulmonary cavities and tuberculous foci. 3) Absence of tuberculous ulcerations in the larynx and gastro-intestinal tract.

One patient in this group had received 67 grams of streptomycin for advanced tracheobronchial tuberculosis which was secondary to chronic pulmonary disease. Treatment was finished 32 days before death. Follow-up bronchoscopy two weeks after treatment revealed healing of the tracheobronchial ulcers. Advanced healing changes with reepithelialization were observed in the ulcers of the trachea and bronchus but areas of active disease were also noted. There was no evidence of intestinal ulceration by gross or microscopic examination.

2. *Cases in Which Resistance was Present or Streptomycin had not been Given for a Long Period of Time (Table II):* There are 20 cases in this group. In evaluating the healing changes within the lungs we believe that it is impossible to differentiate completely changes due to natural healing and those due to streptomycin if the disease has been of long duration. The findings confirm our previous impression that in cases where comparison is possible the pathologic findings indicate approximately when during the treatment the organisms became resistant. As the period of organism resistance or no treatment with streptomycin

TABLE II: Tubercle Bacilli Insensitive at Death or Streptomycin Not Given for Prolonged Period.

	Case No.	Age	Color	Duration of Pul. Tuberculosis in Months	Days of Known Insensitivity	Last Dose; Days Prior to Death	Days Since Last Known Sensitivity	Total Grams of Streptomycin
1.	A-76-49	58	W	9	Postmortem	28	70	21
2.	A-55-59	49	W	48	Postmortem	54	103	42
3.	A-82-49	52	W	132	Postmortem	132	153	67
4.	A-36-49	52	W	7	>49	40	749	42
5.	A-126-49	47	W	192	62	0	86	78
6.	A-113-48	20	W	32	91	0	112	292
7.	A-19-49	22	C	10	62	144	100	43
8.	A-5-50	55	W	12	125	108	142	72
9.	A-7-49	27	C	19	No data	172*	12	99
10.	A-88-49	69	W	72	163	142	207	101
11.	A-32-49	33	C	20	172	235	>172	43
12.	A-61-48	21	C	24	189	171	>189	94
13.	A-118-48	25	W	27	189	171	299	90
14.	A-124-49	33	W	72	194	57	>194	86
15.	A-87-48	23	W	44	209	363	>348	96
16.	A-87-49	29	W	29	262	316	347	118
17.	A-232-49	53	C	34	0	317	0	117
18.	A-16-49	48	W	35	345	0	>345	264
19.	A-25-48	38	W	29	430	319	>430	306
20.	A-11-50	26	C	75	793	354	884	162

	Case No.	Tracheo-bronchial Tree	Larynx	G. I. Tract	Miliary Foci	Perifocal Reaction	Cavity	Extrapulmonary Tuberculosis
1.	A-76-49	0	+	0	Liver.	++	Thin-walled with little healing.	Encapsulated, caseous foci liver; right epididymis.
2.	A-55-59	0	+	+	Kidney, spleen, liver, vertebra.	++	Thick-walled with hyalinization.	Left kidney; pleura.
3.	A-82-49	+	0	0	0	±	Thick-walled; thick caseous lining.	Inspissated empyema cavity.
4.	A-36-49	0	0	0	Liver, spleen, adrenals, kidney, vertebra.	++	Thin-walled with some increase in collagen fibers.	——
5.	A-126-49	Micro. foci left main bronchus.	Micro. foci with healing.	Micro. foci with healing.	Liver, spleen, adrenals, vertebra, with healing.	+	Hyalinization of wall.	——
6.	A-113-48	Micro. foci left main bronchus.	0	+	Spleen, left main bronchus.	+	Thin-walled; lining partially caseous, partially granulation tissue.	Meningitis. Tuberculomata of cerebrum, olfactory bulb.
7.	A-19-49	+	+	0	0	+++	Moderately thick walled with moderate collagenization.	——
8.	A-5-50	+	0	0	Spleen	+	Thick-walled. Caseous with hyalinization.	——
9.	A-7-49	Trachea, left main bronchus, recent, superficial.	Epiglottis, recent, superficial.	+	Liver, spleen, adrenal.	+	Thin-walled with collagenization.	Caseous foci of liver, bile ducts, adrenal, pericardium, spleen, lymph nodes.

*Also received twelve grams in last twelve days. **Silico-Tuberculosis.

(Continued on next page)

TABLE II — CONTINUED

	Case No.	Tracheo-bronchial Tree	Larynx	G. I. Tract	Miliary Foci	Perifocal Reaction	Cavity	Extrapulmonary Tuberculosis
10.	A-88-49	+	+	+	0	++	Old with advanced healing.	——
11.	A-32-49	+	+	+	Liver, spleen, kidney, pancreas, adrenal.	+++	Thin-walled with little healing.	——
12.	A-61-48	0	0	Micro. foci.	Right lung, liver, spleen, kidney, ileum, peritoneum.	+++	Old with thick hyaline walls.	Empyema with sinus tract.
13.	A-118-48	Micro. foci left main bronchus.	+	+	0	+++	Old with thick hyaline walls.	Chronic meningitis.
14.	A-124-49	+	0	Micro. foci.	0	++	Old with advanced healing.	Pleura.
15.	A-87-48	0	0	+	Spleen.	+++	Old with thick hyaline walls.	——
16.	A-87-49	+	0	+	Liver, hepatic bile ducts, spleen, L.L.L., kidney.	+++	Fresh caseous with minimal collagen.	Pleura.
17.	A-232-49	Bronchus, Mediastinal fistula.	Scar.	0	0	+++	Marked collagenization.	Silico-tuberculosis.
18.	A-16-49	0	+	+	Liver, spleen, kidney.	+++	Old with thick hyaline wall.	——
19.	A-25-48	0	+	+	0	+++	Old with thick hyaline walls.	——
20.	A-11-50	+	+	Micro. foci.	Thyroid, liver, spleen, L.L.L.	+++	Thick-walled with hyalinization of walls.	R.L.L. Pleura.

*Also received twelve grams in last twelve days. **Silico-Tuberculosis.

increases the cases become increasingly similar to those which have not received antibiotic therapy.

There are three main criteria which we use to determine a loss of streptomycin effect. 1) The appearance of a wide perifocal reaction, 2) little healing in recent tuberculous foci, and 3) the development of tuberculous ulcers in the upper respiratory and in the gastro-intestinal tracts.

Those cases in which streptomycin therapy has been given for some time and in which the infecting organism became resistant shortly before death showed healing changes in the older pulmonary foci which were out of proportion to the duration of the disease. The more recent foci, however, are surrounded by variably wide zones of perifocal reaction and show no greater tendency toward healing.

Intestinal tuberculosis was present on gross or microscopic examination in 15 (75 per cent) of the 20 cases of which five consisted of microscopic submucosal foci while laryngeal tuberculosis was present in 11 (55 per cent) one of which was microscopic in character. The incidence of intestinal tuberculosis is similar to that in untreated cases while that of laryngeal tuberculosis is actually greater than in untreated cases. These ulcers tend to be more extensive and deeper in those patients whose infecting organisms have been streptomycin resistant for a long time. Our anatomic studies would seem to indicate that tuberculosis within these structures develops relatively shortly after resistance sets in.

In three cases in this group further therapy was attempted after the organisms had become resistant. This was done in an attempt to cure two cases of advanced laryngeal tuberculosis and one case of intestinal disease. At autopsy there was evidence of extensive progression of these lesions in all three cases. In the case of intestinal tuberculosis massive ulcers were found in the ileum. One of these had perforated into the peritoneal cavity.

One of the patients in this group was under treatment for both tuberculous meningitis (duration 20 months) and chronic pulmonary tuberculosis (duration 32 months). The patient received, intermittently, 234 grams of streptomycin (orally and intrathecally) during this period. The meningitis began clinically two months after his first course of streptomycin was discontinued. Subsequently the organisms obtained from the sputum became resistant to 1000 units of streptomycin per cc. three months before his death and remained so on repeated sensitivity determinations. Those organisms obtained from the spinal fluid remained sensitive to death.

The anatomic findings in the lungs were those of anatomic healing in the older foci which were more advanced than would be

TABLE III: Sensitivity Data—Indeterminate.

	Case No.	Age	Color	Duration of Pul. Tuberculosis in Months	Days of Known Insensitivity	Last Dose; Days Prior to Death	Days Since Last Known Sensitivity	Total Grams of Streptomycin
1.	A-124-48	21	C	16	No data	0	150	260
	S-1811-48	"	"	14	"	0	70	180
2.	A-2-49	24	W	9	No data	0	225	296
3.	A-89-49*	28	C	16	No data	1	201	>95
	S-1634-49	"	"	16	"	0	197	>92
4.	A-130-49	27	W	54	No data	151	403	304
5.	A-46-47	20	C	15	Postmortem	93	No data	242
6.	A-153-49	32	C	38	No data	92	247	>43
7.	A-24-50	32	C	108	No data	32	No data	114

	Case No.	Tracheo-bronchial Tree	Larynx	G. I. Tract	Miliary Foci	Perifocal Reaction	Cavity	Extrapulmonary Tuberculosis
1.	A-124-48	+	0	Micro. foci.	Liver.	+++	No cavity.	Pleura, muscle flap, parietal pericardium, mediastinum.
	S-1811-48	No data.	No data.	No data.	No data.	+	Thin-walled but with collagenization.	——
2.	A-2-49	0	0	0	0	±	Thin-walled with collagenization.	Sella turcica, meninges (Far advanced healing with block of Foramina of Luschke).
3.	A-89-49*	0	0	+	Liver.	+++	No cavity.	——
	S-1634-49	No data.	No data.	No data.	No data.	++	Thin-walled with hyalinization.	——
4.	A-130-49	+ Broncho-pleural fistula.	0	Scars.	0	++	Thick-walled with hyalinization.	Prostate.
5.	A-46-47	0	Micro. foci.	Micro. foci.	Liver, spleen, vertebra.	+++	Collagen fibers increased.	——
6.	A-153-49	+	+	+	Kidney.	+++	Thin-walled with collagenization.	——
7.	A-24-50	0	0	0	0	—	Inspissated cavity.	Adrenals; right epididymis and seminal vesicles.

*Massive postpneumonectomy spread.

expected in 32 months. A narrow perifocal reaction was present around the more recent cavities and foci. Superficial ulcerations of recent occurrence were present in the ileum and cecum and a small caseous focus was observed in the left main bronchus.

At the base of the brain were thick yellow zones of caseation which extended for a short distance to the cerebello-pontine angle. The lateral ventricles were widely dilated. Multiple tuberculomata were found in the brain parenchyma.

The microscopic picture of the tuberculous meningitis at the base of the brain was that of a wide layer of caseation surrounded by dense hyalinized connective tissue, while that over the medulla oblongata was of a fibrocellular exudate with zones of caseation. The caseous foci within the brain were also surrounded by dense hyalinized connective tissue.

3. *Those in which Sensitivity Data were Inadequate (Table III):* Seven of our cases are included in this group. The last sensitivity determination on five of these patients were performed at periods varying from 150 days to 403 days before death. All five of these tests showed the organisms to be sensitive to streptomycin. In the sixth case, the only available data showed that the tubercle bacilli were insensitive at death.

In the seventh case tubercle bacilli were not isolated at any time. This patient had developed chronic pulmonary tuberculosis nine years before his death. Within the last year of his life he developed a tuberculous epididymitis and clinical evidence of Addison's disease. He died as a result of the latter disease. He received 114 grams of streptomycin. No sensitivity studies could be performed because material was not obtained for culture. There was anatomic evidence of advanced healing in the adrenals, in the genital organs, and in an inspissated pulmonary cavity. However, there was so much natural healing in this case that an evaluation of the effect of streptomycin on the tuberculous process is impossible.

Another of these cases is of interest in that a pneumonectomy offered an opportunity to compare the status of the perifocal reaction at 70 days with that at 150 days after the last known sensitivity. The pneumonectomy specimen presented a one-plus perifocal reaction while 80 days later, although the patient was still under streptomycin therapy, the perifocal reaction had increased to three-plus.

Another patient received 296 grams of streptomycin for tuberculous meningitis which occurred seven months before his death. The patient developed a block and no fluid was obtainable for sensitivity studies. Death was caused by hydrocephalus due to an obliteration of the foramina of Luschke and Magendie. This obliteration was the result of healing tuberculous meningitis. The

healing changes within the meninges, the healing noted in an accompanying chronic pulmonary tuberculosis of nine months duration, and the absence of laryngeal and intestinal tuberculosis lead us to believe that infecting organisms were still sensitive to streptomycin at the time of death.

Tuberculous Meningitis: Two of the four cases of tuberculous meningitis had received streptomycin therapy over periods of eight months and 25 months respectively. In both cases at the base of the brain were thick caseous masses surrounded by dense layers of hyalinized connective tissue. This is in contrast to untreated cases of tuberculous meningitis in which the greater portion of the exudate was composed of serum, fibrin and cells and only small zones of caseation. Hyalinized connective tissue has never been observed by us in any untreated cases of tuberculous meningitis.

CONCLUSIONS

1) Chronic pulmonary tuberculosis during the period of maximum streptomycin effect is characterized by more rapid healing of tuberculous foci, lack of perifocal reaction about pulmonary foci, and absence of laryngeal and gastro-intestinal tuberculosis.

2) With the onset of resistance, new foci developing in the lungs are similar to those in untreated cases, and intestinal and laryngeal tuberculosis again develop.

3) The treatment of laryngeal and intestinal tuberculosis by streptomycin in cases after the bacilli from tuberculous cavities are resistant is of no value.

4) In one case where tuberculous meningitis and chronic pulmonary disease coexisted, the organisms from the pulmonary lesions became resistant while those from the cerebro-spinal fluid remained sensitive.

5) Tuberculous meningitis in cases treated for long periods is characterized by wide areas of caseation surrounded by broad zones of hyalinized connective tissue.

6) Clinico-pathologic correlation of the effects of streptomycin therapy requires frequent sensitivity studies including postmortem material.

CONCLUSIONES

1) En el periodo durante el cual la estreptomicina ejerce su efecto máximo se caracteriza la tuberculosis pulmonar crónica por los siguientes efectos: cicatrización más rápida de los focos tuberculosos, falta de reacción perifocal alrededor de los focos pulmonares y ausencia de tuberculosis laríngea y gastrointestinal.

2) Con el desarrollo de resistencia los nuevos focos que aparecen en los pulmonaes son semejantes a los de los casos no tratados y

se desarrolla de nuevo la tuberculosis intestinal y laríngea.

3) El tratamiento de la tuberculosis laríngea e intestinal con la estreptomicina no tiene valor en casos en los que ya son resistentes los bacilos en las cavernas tuberculosas.

4) En un caso en el que coexistían la meningitis tuberculosa y la tuberculosis pulmonar crónica, los organismos de las lesiones pulmonares se volvieron resistentes mientras que los del líquido céfalorraquídeo permanencieron sensibles.

5) La meningitis tuberculosa, en casos tratados por largos períodos, se caracteriza por anchas zonas de caseificación rodeada de vastas zonas de tejido conectivo hialinizado.

6) La correlación clínicopatológica de los efectos de la estreptomicino terapia necesita frecuentes estudios de sensibilidad inclusive de material autópsico.

REFERENCES

1 Baggenstoss, A. H., Feldman, W. H. and Hinshaw, H. C.: "Streptomycin in Miliary Tuberculosis," *Am. Rev. Tuberc.*, 55:54, 1947.
2 Rich, A. R.: "The Pathogenesis of Tuberculosis," *Charles C. Thomas*, Springfield, Illinois, 1944.
3 Kidd, J. G.: "Modifications of Tuberculous Lesions in Patients Treated with Streptomycin," *Bull. New York Acad. Med.*, 24:132, 1948.
4 Flory, C. M., Correll, J. W., Kidd, J. G., Stevenson, L. D., Alvord, E. C. Jr., McDermott, W. and Muschenheim, C.: "Modifications of Tuberculous Lesions in Patients Treated with Streptomycin," *Am. Rev. Tuberc.*, 58: 421, 1948.
5 Auerbach, O. and Stemmermann, G. N.: "Anatomic Changes in Tuberculosis Following Streptomycin Therapy," *Am. Rev. Tuberc.*, 58:449, 1948.
6 Silverthorne, M. D. and Silverman, G.: "The Effect of Streptomycin on the Morphology of the Tuberculous Lesion," *Am. Rev. Tuberc.*, 61:525, 1950.
7 Mahon, H. W.: "Pathology of Pulmonary Tuberculosis: As Modified by Streptomycin Therapy," *Am. Rev. Tuberc.*, 61:543, 1950.

The Effect of Heat on Streptomycin and Para-Aminosalicylic Acid in Tuberculosis Culture Medium*

MARGARET C. DRUMMOND, M.S., GEORGE T. LEWIS, Ph.D.
and MARTIN M. CUMMINGS, M.D., F.C.C.P.
Chamblee, Georgia

Because different methods of determining the sensitivity of tubercle bacilli to streptomycin utilize media which may or may not be heated for coagulation, and because often different levels of sensitivity are obtained when the same organism is tested on different media, an investigation of the effects of heat on streptomycin in the presence of a complex egg medium was initiated. Waksman and co-workers[1] first reported that streptomycin is biologically inactivated in acid and alkaline solutions, and that 50 per cent of its activity is lost in 50 minutes at 100 degrees C.

Regna et al,[2] studying the stability of streptomycin, reported that, whereas the drug is relatively stable at or below room temperature, drastic decomposition occurs at 95 degrees C., 50 per cent of the drug being destroyed in 4½ hours. Henry, Berkmann and Housewright,[3] investigating the loss of streptomycin in various culture media incubated at 4, 30 and 37 degrees C., employed a biological method, and found a decrease as great as 58 per cent in 24 hours.

Since the classical tuberculosis egg media require heating (for 1 hour) at 85 to 90 degrees C. for coagulation, it was suggested by William Steenken, Jr. at the Trudeau Foundation, Saranac Lake, New York, that accurate information be obtained as to the effects of this heating on streptomycin added to potato flour-egg medium in the amounts routinely employed in the assay procedure. Since bio-assays are notoriously insensitive when small amounts of the drug are tested, it was decided to employ chemical methods for the determinations.

During the work involving streptomycin, it became obvious that the same problem exists in determining the sensitivity of tubercle bacilli to para-aminosalicylic acid (PAS) and studies of the inactivation of this drug in the presence of culture medium were also performed.

---

*From the Tuberculosis Research Laboratory, Lawson Veterans Administration Hospital, Veterans Administration, Chamblee, Georgia, and Department of Medicine, Emory University School of Medicine, Atlanta. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Experimental Methods and Results

1) *Streptomycin:*

Concentrations of streptomycin greater than 500 mcgm. per ml.: The colorimetric method of Boxer and Jelinek[4] based on maltol formation, was employed with ferric ammonium sulfate as the color reagent since the concentrations of streptomycin fell within the range of sensitivity for this reagent. Several modifications in this procedure were made to render possible quantitative recoveries of the drug from a medium as complex as that of Lowenstein-Jensen. Because of the instability of streptomycin in acid solution, (acid catalyzes the hydrolysis of the streptomycin molecule into its basic fractions, streptidine and streptobiosomine), it was necessary to substitute the $ZnSO_4$-NaOH method of protein precipitation, described by Boxer and Jelinek for photofluorometric determinations of streptomycin in blood[5] in place of the customary acid deproteinizing agent, trichloroacetic acid. Deproteinization in this manner yielded a protein-free, yet cloudy supernatant layer, which was clarified only by extraction with equal volumes of chloroform. Streptomycin is not appreciably soluble in chloroform, since repeated standard calibration curves, employing the chloroform extraction technique, duplicated consistently those obtained with simple aqueous solutions of streptomycin.

Recoveries of streptomycin from the culture medium prior to inspissation were carried out by the dilution of 5.0 ml. aliquots of the drug-containing medium with 10.0 ml. of water and precipitation with 10.0 ml. of 10 per cent $ZnSO_4$ and 0.5N NaOH respectively. The sample was then centrifuged and the supernatant shaken with an equal volume of chloroform (C.P.). Centrifugation then yielded a clear supernatant layer, aliquots of which were removed for streptomycin determination by means of the maltol method.

Analytical recoveries of streptomycin added to the liquid culture medium were determined in this manner on a number of different samples and on more than one lot of the medium. Recoveries obtained when the concentration of streptomycin was 1000 mcgm. per ml. averaged 95.1±7.1* per cent for 12 samples, and 95.6±4.9 per cent for 11 samples for a concentration of 500 mcgm. per ml.

Determination of the streptomycin content of the egg medium after inspissation necessitated a preliminary homogenization before the deproteinization could be effected. The medium had previously had 100, 500, and 1000 mcgm. per ml. of streptomycin added, and dispersed in 5 ml. aliquots per tube. The contents of

*This and subsequent corresponding figures represent the extreme of variations from the average.

the tubes were then coagulated by inspissation for 1 hour at 85 degrees C. in an electric inspissator. The contents of a single tube of medium (containing 5 ml. of 500, or 1000 mcgm. of streptomycin per ml.) were quantitatively transferred to a Ten Broeck tissue grinder for homogenization, dilution and protein precipitation.

Table I shows the results of streptomycin determinations on the inspissated egg medium. The mean percentage recovery for a series of eight determinations (1000 mcgm. per ml.) was 56.1, or a total loss of streptomycin of 43.9 per cent and for a series of seven (500 mcgm. per ml.) was 52.6, or a loss of 47.4 per cent.

Concentrations of streptomycin less than 500 mcgm. per ml.: Theoretically, it was desirable to show the loss of streptomycin in each of the concentrations employed in the sensitivity assay method, that is, 1, 10, 100 and 1000 mcgm. per ml. The methods of analysis available in the literature, however, either were not sufficiently sensitive for levels of this low order, or were not adaptable because of the preponderance of interfering substances in the egg-potato flour medium. Eiseman's modification[6] of the

TABLE I

Analytical Recoveries of Streptomycin from Lowenstein-Jensen Medium After Inspissation at 85 Degrees C. for One Hour.

Original Streptomycin content mcgm./per ml.	Streptomycin content after dilution mcgm./per ml.	Streptomycin recovered after dilution mcgm./per ml.	Percentage recovery with deviation from average
1000	142.8	81.0	56.7+ 0.6
1000	142.8	77.0	54.0− 2.1
1000	142.8	71.5	50.0− 6.1
1000	142.8	88.0	61.5+ 5.4
1000	142.8	75.0	52.5− 3.6
1000	142.8	86.0	60.5+ 4.4
1000	142.8	83.0	58.1+ 2.0
1000	142.8	79.0	55.5− 0.6
500	71.4	33.8	47.5− 5.1
500	71.4	31.3	41.0−11.6
500	71.4	41.5	58.0+ 1.4
500	71.4	41.5	58.0+ 1.4
500	71.4	37.8	53.0+ 0.4
500	71.4	41.5	58.0+ 5.4
500	71.4	37.8	53.0+ 0.4

maltol method was found to be applicable to the 100 mcgm. per ml. concentration; the maltol being separated from interfering substances in the medium by steam distillation, and the blue color formed with the Folin-Ciocalteau phenol reagent which is more sensitive than the ferric ammonium sulfate reagent. Because of the necessary dilutions in deproteinization, it was impossible to determine streptomycin on concentrations of less than 100 mcgm. per ml. by this maltol method.

The method of analysis of the 100 mcgm. per ml. concentration consisted of: deproteinization by the $NaSO_4$-NaOH method, maltol formation, maltol distillation and color formation with the phenol reagent. Recoveries of streptomycin from the liquid culture medium prior to heating averaged 95.6±6.9 per cent for a series of six samples. Table II shows the results of determinations on the inspissated medium; in concentrations of 100 mcgm. per ml. in culture medium heated at 85 degrees C. for one hour, the streptomycin loss was found to be 47.0 per cent.

2) *Para-aminosalicylic acid:*

The diazotization method of Bratton and Marshall[7] for determination of PAS in blood was applied to both liquid and solid egg medium with only a modification of dilution. PAS is stable in acid solution, and therefore trichloroacetic acid protein precipitation was employed. If the protein were precipitated directly from an undiluted sample of the medium containing PAS, a cloudy, nonprotein supernatant layer formed, which rendered impossible the use of a colorimetric method. Application of the chloroform extraction technique employed for the streptomycin assays yielded

TABLE II

Analytical Recoveries of Streptomycin from Lowenstein-Jensen Medium After Inspissation at 85 Degrees C. for One Hour. (Maltol Distillation Method)

Original Streptomycin content mcgm./per ml.	Streptomycin content after dilution mcgm./per ml.	Streptomycin recovered after dilution mcgm./per ml.	Percentage recovery with deviation from average
100	80	37.1	46.5—6.5
100	80	43.5	54.0+1.0
100	80	40.0	50.0—3.0
100	80	43.5	54.0+1.0
100	80	47.0	58.5+5.5
100	80	43.5	54.0+1.0

inconsistent, non-quantitative results, due probably to the solubility of PAS in the chloroform layer. Dilution of the medium 1 to 3 with water prior to deproteinization produced a clear supernatant layer.

Recoveries of PAS added to the liquid medium were carried out using dilutions of 0.5, 1.0 and 10.0 mg per cent PAS. On a series of 7 determinations, the mean percentage recoveries were 94.1± 4.9 per cent for the 0.5 mg per cent concentration, 97.0±5.0 per cent for a series of 12 of the 1.0 mg. per cent concentration and 99.2±48 per cent for a series of 6 of the 10.0 mg. per cent concentration.

The preparation of samples of the PAS-containing egg medium, coagulated by inspissation, was carried out in the manner prescribed for streptomycin determination. The contents of the tubes, containing 5.0 ml. of medium with PAS incorporated, were quantitatively transferred to a Ten Broeck grinder for homogenization, dilution and protein precipitation using 15 per cent trichloroacetic

TABLE III

Analytical Recoveries of PAS from Lowenstein-Jensen Medium After Inspissation at 85 Degrees C. for One Hour.

Original PAS content Mg. per cent	PAS content recovered after dilution Mg. per cent	PAS content after dilution Mg. per cent	Percentage recovery with deviation from average
0.5	0.094	0.1	94.0−0.3
0.5	0.099	0.1	99.0+4.7
0.5	0.090	0.1	90.0−4.3
1.0	0.195	0.2	97.5+0.1
1.0	0.209	0.2	103.0+9.6
1.0	0.190	0.2	95.0−2.4
1.0	0.190	0.2	95.0−2.4
1.0	0.286	0.3	95.5−1.9
1.0	0.282	0.3	96.5−0.9
1.0	0.279	0.3	96.0−1.4
1.0	0.300	0.3	100.0+2.6
10.0	0.478	0.5	95.6−1.8
10.0	0.450	0.5	90.0−7.4
10.0	0.520	0.5	104.0+6.6
10.0	0.520	0.5	104.0+6.6
10.0	0.505	0.5	101.0+3.6

acid. After centrifugation, 10.0 ml. of the supernatant was removed for PAS analysis according to the Bratton-Marshall technique.

The results of determinations on inspissated culture medium containing graded amounts of PAS are given in Table III. The mean recovery of PAS from medium containing 0.5 per cent was 94.3±9.0 per cent, from medium containing 1.0 mg. per cent was 97.4±2.6 per cent, and from medium containing 10.0 mg. per cent was 99.4±9.4 per cent.

Discussion

It is evident that in preparing streptomycin-containing medium which is coagulated by heating, one must compensate for the chemical loss by adding sufficent amounts of the drug to give the desired final concentrations. This does not seem to be necessary in the preparation of PAS containing medium, since there has been found to be no appreciable loss of PAS due to the heat of inspissation. It must be emphasized, however, that recoveries of a drug by chemical methods may not necessarily reflect its biological activity, since factors, such as physical binding by certain substances in the medium, are not taken into account. However, biological assays of streptomycin tested against freshly isolated strains of tubercle bacilli, indicate that chemical loss of the drug is accompanied by a similar loss in biological activity. This probably explains discrepancies in sensitivity tests performed in various laboratories employing different culture techniques.

SUMMARY

1) By chemical methods it was found that the concentrations of streptomycin in egg culture medium of 100, 500, and 1000 mcgm. per ml., only 51.8, 52.6 and 56.1 per cent respectively of the drug was recoverable after heating at 85 degrees C. for one hour.

2) PAS was found to be relatively stable to the heat of inspissation, 94.3 to 99.4 per cent being recoverable from inspissated egg medium.

3) From this study it would seem necessary to compensate for the loss of streptomycin in preparing known concentrations of the drug for assay purposes when a medium is employed which requires heat for coagulation.

Acknowledgment: This study was begun with the encouragement and advice of William Steenken, Jr., at whose laboratory some of the initial work was performed.

RESUMEN

1) Empleando métodos químicos se descubrió que, de concentraciones de estreptomicina de 100, 500 y 1000 mcgm. por ml. en

medio de cultivo de huevo, sólo se pudo recobrar el 51.8, 52.6 y 56.1 por ciento, respectivamente, de la droga, después de calentarlos a 85° C. por una hora.

2) Se encontró que el PAS es relativamente estable cuando se le somete al calor de espesamiento, recobrándose del 94.3 al 99.4 por ciento del medio de huevo espeso.

3) De este estudio se deduce que parece ser necesario compensar por la pérdida de estreptomicina, cuando se preparan concentraciones conocidas de la droga para ensayo y se emplea un medio que necesita calor para coagularlo.

REFERENCES

1 Waksman, S. A., Bugie, E. and Schatz, A.: "Isolation with Special Reference to Streptothricin and Streptomycin of Antiobiotic Substances from Soil Micro-Organisms," *Proc. Staff Meet., Mayo Clinic*, 19:537, 1944.

2 Regna, Peter, Wasselle, Leonard and Solomons, I. A.: "The Stability of Streptomycin," *J. Biol. Chem.*, 165:631, 1946.

3 Henry, R. J., Berkmann, S. and Housewright, R. D.: "Studies of Streptomycin. II. Inactivation of Streptomycin Upon Standing in Certain Culture Media and Human Serum," *Jour. Pharm. Exp. Therapy*, 90: 42, 1947.

4 Boxer, George and Jelinek, Viola: "Coloremetric Determinations of Streptomycin in Clinical Preparations, Urine and Broth," *J. Biol. Chem.* 169:153, 1947.

5 Boxer, George and Jelinek, Viola: "Chemical Method for the Determination of Streptomycin in Blood and Spinal Fluid," *J. Biol. Chem.*, 170: 491, 1947.

6 Eiseman, William: "Spectrophotometric Method for Determining Streptomycin," *Anal. Chem.*, 21:1507, 1949.

7 Marshall, E. K.: "Determination of Para-aminosalicylic Acid in Blood," *Proc. Soc. Exper. Biol. Med.*, 68:471, 1948.

Spontaneous Rupture of the Esophagus*

M. EUGENE FLIPSE, M.D.
Miami, Florida

Spontaneous rupture of the esophagus is one of the rarer yet more dramatic conditions for which the recent advances of thoracic surgery and antibiotic therapy have offered a means of definite treatment and cure. Although the condition was first described by Boerhaave[15] in 1724 and since then has been reviewed by Fitz (1877),[30] McKenzie (1884),[57] Walker (1914),[84] Smead (1931),[77] Girard (1934),[35] Ridgeway and Duncan (1937),[70] Terracol (1938),[78] Barrett (1946),[6] and Kinsella, Morse and Hertzog (1948),[47] it is still not widely recognized. It would seem worth while to consider certain aspects of the problem which should lead to its earlier diagnosis for if the condition is suspected its presence can be readily substantiated and prompt surgical therapy instituted.

Definition and Classification

Under the heading of spontaneous rupture of the esophagus should be grouped all patients with rupture or perforation of that organ due to an increase in the intraesophageal pressure greater than the tensile strength of the wall. Excluded are patients in whom there is clinical or gross pathological evidence of preexisting disease (congenital defects, diverticula, tuberculosis, cancer), or of trauma (gunshot and stab wounds, foreign body, instrumentation with esophagoscope, gastroscope, bougie or dilator), at the site of rupture. This broad definition which includes cases with clinically silent inflammations, ulcerations and softening is not acceptable to some authors[6,28,30,84] who insist on complete normalcy of the esophagus at the time of rupture. Their opinion does not seem valid for it is frequently impossible even at autopsy to be certain that the esophagus was normal,[30,42,93] and further, the clinical problems of diagnosis and therapy are frequently the same in both cases.[20,21,48]

It is helpful to divide the cases of spontaneous rupture into two groups. In the first are those patients in whom the esophagus is allegedly normal prior to rupture and in whom the increased intraesophageal pressure is the only factor producing the rupture. In the second group the clinically silent, frequently only micro-

*Presented in part at the Seventh Annual Meeting of the Southern Chapter of the American College of Chest Physicians, Cincinnati, Ohio, November 13, 1949. From the Department of Pathology, Ph. R. Rezek, M.D., Director, Jackson Memorial Hospital, Miami, Florida.

scopic disease predisposes to rupture by weakening the wall. Certain of the patients in the latter group may be suffering from serious extraesophageal disease which alters the clinical picture but in general the syndrome is the same in both groups. With these two groups in mind the reports of spontaneous rupture of the esophagus in many apparently unrelated conditions and the multiple theories advanced to explain its occurrence fall into one general schema, involving the relationship of intraesophageal pressure and esophageal strength.

Pathogenesis of Rupture

In the production of increased intraesophageal pressure the factors of increased intraabdominal pressure, patency of the cardia, distention of the stomach and obstruction of the esophagus all play important roles. Since the esophagus is normally an empty tube any increase in intraesophageal pressure must be secondary to increased intraabdominal pressure with transmission of this pressure by the stomach contents through the cardia into the esophagus. Whether the pressure reached will be sufficient to rupture the esophagus will depend upon the strength of the esophagus and the intensity of the increase in intraesophageal pressure. The latter will depend on the rapidity and magnitude of the increased intraabdominal pressure, the amount of stomach contents and the patency of the cardia and esophagus. Vomiting and retching from any cause are the most important causes of sudden increased intraabdominal pressure but pressure increases great enough to produce rupture of the esophagus have also resulted from the straining associated with defecation, lifting and convulsing and from blunt trauma to the abdomen.

If the cardia does not open, at least in part, the increased pressure will produce multiple circumferentially arranged lacerations of the cardia which occasionally extend into the adjoining portion of the esophagus. Mallory and Weiss[55,89] have described the syndrome associated with these lacerations, seen following prolonged vomiting in chronic alcoholism or pregnancy and characterized by recurrent, frequently fatal, massive hematemasis but rarely perforation.

The transmitted force of sudden increased intraabdominal pressure can only produce significantly increased intraesophageal pressure if the contents of the stomach can not be expelled through the esophagus as rapidly as they leave the stomach. This disportion between esophageal filling and emptying can occur either because of distention of the stomach with food or fluid or because of obstruction of the esophagus. Analysis of the reported cases suggests that in some, distention of the stomach may have been

the determining factor, for rupture occurred at a time when the stomach was full or over distended and not previously when all the other factors were present. Rupture proximal to mechanical obstruction of the esophagus from external pressure by mediastinal tumor, goiter or nodes, or from an impacted bolus of food or from a stricture with or without impacted food is not unknown[30,59,60,88] and shows the role obstruction can play in preventing or delaying the reduction of increased intraesophageal pressure produced by vomiting and/or retching. However, in the majority of cases no mechanical obstruction is present. Therefore, obstruction due to physiological mechanisms is postulated. The complex anatomical makeup of the esophagus and the highly complex nature of the vomiting reflex make this concept quite tenable. Anatomically[14,23] the esophagus is narrowest at the esophageopharyngeal junction where it passes through the restricted space between the cricoid cartilage anteriorly and the sixth cervical vertebra posteriorly. It is also at this level that the longitudinal bands of muscle fibers fan anteriorly to their tendinous insertion on the posterior surface of the cricoid cartilage, leaving the heavier circular muscle fibers the predominate musculature of the upper portion of the esophagus. These circular fibers fuse anatomically and functionally with the lower border of the inferior constrictor muscle of the pharynx forming a muscular sphincter at this level. The musculature of the pharynx, upper esophagus and diaphragm is striated and as such has motor innervation which is solely excitatory in nature whereas the musculature of the lower esophagus and remainder of gastrointestinal tract is smooth with both inhibitory and excitatory innervation through the autonomic nervous system. This difference in innervation and muscle type predisposes to inherently greater tonicity of the striated muscles at all times and to actual spasm during any generalized motor discharge as occurs during the convulsions of epilepsy or intracranial disease.

Vomiting is a complex reflex act requiring the synchronous relaxation and/or contraction of many voluntary and involuntary muscles.[11,41] It is under the control of the vomiting center, a group of cells in the sensory nucleus of the vagus which is located in the floor of the fourth ventricle. This center may be stimulated directly by many drugs and toxins, by partial asphyxia, by increased intracranial pressure, as well as by the usual means of reflex stimulation from various organs of the body, especially the gastrointestinal tract and organs of special senses. In common with other nerve cells, it may become fatigued from too continuous or excessive stimulation, producing incoordination of the vomiting reflex. Incoordination of the vomiting reflex has been seen as a

result of prolonged vomiting[58] and in acute and chronic alcoholism.[53] It probably occurs at times with heavy sedation, anesthesia, acidosis, alkalosis, and diseases of the central nervous system either by their direct action on the center or indirectly through production of anoxia or cerebral edema and resulting increased intracranial pressure. Such incoordination could result in physiological obstruction of the esophagus at either its upper or lower portion. If the esophageal hiatus did not widen by a change in position and tone of the diaphragm and the cardia did not relax, the stage would be set for the development of the Mallory-Weiss syndrome whereas if the pharyngeal passage did not widen by the drawing forward of the larynx and the hyoid bone and the circular muscles of the upper esophagus and lower pharynx did not relax, conditions would favor rupture of the esophagus.

While the purely mechanical aspects of esophageal rupture are relatively clearcut and generally accepted the subject of alterations of the wall of the esophagus which produce weakness and so predispose to rupture is filled with theory and disagreement. Esophagitis (acute and chronic)[8,13,82] simple (peptic) ulcer of the esophagus[32,46,54,79] and esophagomalacia[58,72,94] are related conditions with many common etiological factors. In all three a most important factor seems to be the action of the gastric juice upon a tissue which has lost its normal resistance to the enzymic action of the digestive ferments.[14] In 1869 Pavy[67] suggested that this loss of resistance was due to interference with the normal circulation of blood through the wall of the gastrointestinal tract. Subsequent experiments and clinical observations have supported this theory. Thus esophagitis and ulcer have been reported as a result of vascular occlusion from arteriosclerosis, syphilis, embolism, thrombosis and spasm as well as from chronic venous congestion from heart failure or portal hypertension. The poor state of the circulation in shock from any cause and in the terminal stages of many diseases is felt to contribute to the esophageal changes frequently found in these conditions.[68] Prolonged or repeated contact of the gastric juice upon this devitalized tissue is favored by retching, vomiting and relaxation of the cardia.[5,32] The latter may be due to nausea, gastric dilatation secondary to pyloric obstruction, or from reflex changes secondary to diseases of the central nervous system. Hyperthermia which enhances digestion, surface irritants such as tubes, alcohol, excessive heat or cold, and miscellaneous factors such as foci of infection, deficiency states and aberrant gastric mucosa may be contributing factors in certain cases.[31,32,46]

Esophagomalacia or intravital softening of the esophagus was

first clearly differentiated from post mortem softening by Rokitansky[72] in 1849. He pointed out its occurrence either as a part of the terminal cachexia of various diseases or as a complication of acute and chronic diseases of the central nervous system. In the former cases the process is extensive and is rapid in its progression. In these it represents merely the premature onset of post mortem changes and as such has little place in a consideration of spontaneous rupture of the esophagus, for while rupture into the mediastinal and pleural spaces frequently occurs, it is noted as a hardly perceptible decline in an already moribund patient and has no therapeutic possibilities. The esophagomalacia associated with diseases of the central nervous system is frequently focal in nature and gradual in progression. Its presence helps to explain the relatively high incidence of spontaneous rupture of the esophagus in these conditions as emphasized in the past by Cushing,[24] Masten and Bunts,[55] Opper and Zimmerman[65] and more recently by Fincher and Swanson.[29] Its presence and the more frequent gastromalacia has been seen associated with different congenital, inflammatory, neoplastic and traumatic diseases of the brain and its coverings. The clinical observations[24,55] and experimental studies[9,25,44,50,87] have emphasized the importance of stimulation of the mid brain and hypothalamic nuclei in the development of esophagomalacia and gastromalacia but disease of any portion of the brain can lead to their development[65] perhaps through influence on these centers. The bulk of experimental work suggests that the theory of spastic ischemic postulated by Zenker and Ziemssen[94] in 1878 is valid for ischemia, then diapedesis of red blood cells, and finally softening have been observed by different workers[9,44,50,87] using different methods of central nervous system stimulation. Thus esophagomalacia appears to be a noninflammatory esophageal softening due to the action of gastric juice on a tissue made ischemic by nervous stimulation. Its presence, or the presence of esophagitis or ulceration would greatly weaken the esophageal wall and so predispose to rupture.

Etiology

The etiology of spontaneous rupture of the esophagus has been suggested in the discussion of the pathogenesis of the rupture. It is seen chiefly in association with vomiting and/or retching, alcoholism and diseases of the central nervous system. In all of these conditions there are multiple factors present leading to both increased intraesophageal pressure and weakness of the esophageal wall. Table I lists the specific conditions with which spontaneous rupture of the esophagus has been found. Of necessity there is some overlaping of etiology in this table. For convenience

TABLE I

SPONTANEOUS RUPTURE ASSOCIATED WITH

I. *Central Nervous System Disease.*
- A. Congenital
  - 1. Internal hydrocephalus[12,72,94]
- B. Inflammatory
  - 1. Meningitis
    - a. Tuberculosis[12,72,94]
    - b. Pneumococcus[65]
    - c. Meningococcus[37]
    - d. Post-operative[65]
  - 2. Encephalitis
    - a. Poliomyelitis[47]
    - b. Measles[65]
    - c. "Viral"[55]
  - 3. Syphilis
    - a. Paresis[36]
    - b. Gumma[45]
- C. Tumors
  - 1. Primary
    - a. Malignant
      - (1) Cerebellar*[24]
    - b. Benign
      - (1) Craniopharyngioma*[29,65]
      - (2) Meningioma
        - (a) Frontal*[29]
        - (b) Sphenoid ridge*[29]
  - 2. Metastatic
    - a. Frontal lobe*[65]
- D. Trauma
  - 1. Skull fracture
    - a. Basal[59]
    - b. Fronto-Temporal*[91]
  - 2. Extradural hematoma[62,65]
  - 3. Gunshot[65]
- E. Vascular
  - 1. Arteriosclerosis (Case 2)
- F. Craniotomy[24,29,63,65,91]
- G. Epilepsy[45]

*Craniotomy.

II. *Vomiting and/or Retching.*
- A. Overindulgence of food and alcohol[6,16,47,70]
  - 1. Reflex
  - 2. Self induced
- B. Gastrointestinal tract disease[3,28,47]
- C. Impacted food bolus
  - 1. Stricture[60,88]
  - 2. No stricture[30,59]
- D. Metabolic Disease
  - 1. Addison's disease[17]
  - 2. Diabetes mellitus[95]
- E. Post-operative
  - 1. Abdominal
    - a. Gastrointestinal[28,37]
    - b. Pelvic[7]
  - 2. Neurological[24,29,63,65,91]
  - 3. Amputation[73]
- F. Miscellaneous
  - 1. Sea Sickness[76]
  - 2. Shell fish intoxication[35]

III. *Miscellaneous.*
- A. Lifting[30,83]
- B. Defecation[92]
- C. Blunt Trauma
  - 1. Chest[63,88,34]
  - 2. Abdomen[4,88]
- D. Burns[69,71]
- E. Minimal
  - 1. Large meal[6]
  - 2. Glass of water[52]
- F. Nothing[17,49,47,61]

---

the postoperative cases are included with the vomiting group although it is true that vomiting was only one of several important factors in these cases. It will be argued that certain of the cases listed in the central nervous system disease group represent terminal esophagomalacia rather than spontaneous rupture of the esophagus for where any doubt existed they were included in the tabulation under rupture.

Pathology

The pathological findings at autopsy or surgery will vary somewhat depending on the presence or absence of preexisting disease of the esophagus, the interval between rupture and observation, and the course followed after the initial rupture of the esophageal wall. The tear is usually single, longitudinal and just above the cardia. Its edges may be clean cut, "as if cut by a knife," or ragged and ulcerated. The rupture is usually on the left posterolateral wall into the left pleural space where the esophagus has the least external support. It is frequently impossible to determine the previous status of the esophagus if death or surgery is delayed for more than several days. These findings agree with the experimental observations of Zenker and Ziemssen,[94] McKenzie,[57] Brosch,[18] Duval,[27] and Burt[19] which have recently been reviewed and corroborated by Kinsella, Morse and Hertzog.[47] All of these workers, using various techniques, found that the lower one third of the esophagus was the weakest portion of the organ, that it was more susceptible to sudden increased pressure than to gradual increased or sustained pressures and that the mucous membrane offered greater resistance to stress than did the muscular coats. Rupture was usually single and longitudinal. Although the exact pressure required to produce rupture varied somewhat, depending on the techniques used, it was within a range obtainable by physiological mechanisms such as vomiting or straining.

Once rupture of the esophagus has occurred the subsequent course of the stomach contents and air that pass through the rent is variable. If there are adhesions between the pleura and

the esophagus at the site of rupture, perforation directly into the pleural space without contamination of the mediastinum will occur. This gives rise to a hydropneumothorax, frequently of a tension type. If the process remains localized in the mediastinum, mediastinal emphysema and subcutaneous emphysema rapidly develop. The mediastinitis, at first chemical and later bacterial, causes the rapid development of sterile or septic pleural effusion and usually in a matter of hours, ruptures into one or both pleural spaces, occasionally at a higher level than the rent in the esophagus. These events give rise to a marked mediastinitis with or without abscess formation and to an empyema with or without necrosis of the underlying lung. The marked collapse and toxicity and the death of at least 70 per cent of these patients within the first 24 hours, is ascribed to the violence of the chemical mediastinitis and/or pleuritis, and to the marked interference with cardio-respiratory function from the mechanical compression of the vascular structures in the mediastinum as a result of the high pressures in the mediastinal and/or pleural space.

Clinical Aspects

The clinical picture of spontaneous rupture of the esophagus varies somewhat, depending on whether it occurs in a previously normal person, in a post-operative patient or in a neurosurgical patient. In the former, where the mechanical factors predominate, the picture is quite uniform and usually most violent. The patient, a middle aged male, usually a chronic alcoholic, frequently with chronic dyspepsia, during vomiting and/or retching usually after recent overindulgence in food or alcohol, has sudden onset of pain, collapse, respiratory distress, upper abdominal rigidity, and later subcutaneous emphysema.

The vomiting, either reflex or self induced, is frequently violent and prolonged. The vomitus often contains small amounts of bright red blood or "coffee ground" material but never large amounts of blood. The vomiting usually ceases with the onset of pain. In a few cases there is no antecedent vomiting and in a rare case there is no apparent precipitating factor.

The pain is usually excruciating and continuous, unrelieved by large doses of opiates, but may be minimal or even absent. It usually is substernal or high in the epigastrium, radiating through to the back or lower thoracic area, more frequently the left, or to the shoulder area. The pain may be most severe in the back or renal areas, with little radiation. The pain is frequently so severe that the patient cannot remain quiet, frequently preferring to sit leaning forward with arms clasped about the chest, or to lie on the effected side with the knees drawn up to the chest.

Some patients describe a sensation of "something giving way," or "tearing," or "bursting" in the lower chest at the onset of the pain.

Evidence of collapse is usually an early and prominent finding but may be minimal and late. Most patients have pale, cool, clammy, sweaty skins, frequently with slight cyanosis. The pulse is usually weak and rapid and the blood pressure may be low. Thirst may be marked in a few cases. The temperature is usually normal or subnormal during the initial hours but then begins to rise. This collapse does not respond particularly well to usual shock therapy, suggesting that it may be due chiefly to mechanical interference with cardiac function.

Respiratory findings of rapid, labored, grunting, shallow respiration with slight cyanosis and dyspnea may or may not be prominent at onset, but become progressively more apparent during the initial hours of the disease. Chest signs are frequently not carefully sought for because of the critical condition of the patient and the more obvious abdominal signs, but even if careful physical examination of the chest is made, they may not be apparent in the first few hours. Then rales, changes in percussion note and breath sounds appear, followed by the signs of hydrothorax, hydropneumothorax or tension hydropneumothorax.

The abdominal signs which may predominate the early hours of the disease have quite understandably led to the erroneous diagnosis of perforated peptic ulcer, for there may be marked upper abdominal spasm, rigidity and tenderness. The lower abdomen is normal, as is the rectal examination.

Subcutaneous emphysema, at first deep in the supraclavicular and suprasternal spaces and later more generalized, appears in about two thirds of the patients. It is seen within the first few hours if the process is confined for a time in the mediastinum but is seen later if there is early rupture into the pleural space. In the latter case it will not develop until the pressure of the hydropneumothorax has reached or exceeded atmospheric pressure making it as easy for the gas to pass into the fascial planes of the mediastinum as to escape into the pleural cavity. In a few patients, subcutaneous emphysema is the presenting symptom, the pain, collapse and other symptoms being minimal or absent. It is the one finding which most suggests but does not prove the presence of a ruptured esophagus.

In the post-operative patients and in patients suffering from serious extraesophageal disease the rupture is primarily due to weakness of the esophageal wall. In these patients, the accident is frequently less fulminating because the violent vomiting and resulting high pressure changes in mediastinal and pleural spaces

are often lacking. In these patients, the clinical picture is variable, showing the features of the underlying disease combined with any of the features of the rupture syndrome.

Cushing[24] and more recently Fincher and Swanson[29] have clearly described the clinical picture of spontaneous rupture of the esophagus as a complication of craniotomy. They noted that, although the immediate post-craniotomy reaction was satisfactory with the expected but relatively stationary increase in temperature, pulse and respiration, in the first eight to 12 hours as recovery from the anesthetic hynosis occurred, vomiting of bright red or changed blood began. Consciousness, partly or completely regained by the end of the first day began to lag and the patient lapsed into stupor and then coma over a four to six hour period. This change in consciousness, which was the only new neurological finding, was associated with extreme restlessness, excessive sweating, cyanosis of fingers and toes, dyspnea and increase of pulse and respiratory rate. The immediate temperature reaction to craniotomy which had begun to fall prior to the onset of these symptoms, rose abruptly and continued to rise in spite of antipyretic therapy usually effective in controlling post-craniotomy hyperthermia. Subcutaneous emphysema did not develop and the blood pressure remained normal until just prior to death which usually occurred within 48 hours of craniotomy.

Differential Diagnosis

The differential diagnosis of spontaneous rupture of the esophagus is complex, involving a consideration of all intrathoracic and upper abdominal emergencies. These include coronary thrombosis, dissecting aneurysm of the aorta, spontaneous pneumothorax, spontaneous hemopneumothorax, spontaneous mediastinal emphysema, pulmonary embolism, massive collapse of the lung, ruptured peptic ulcer, acute pancreatitis, mesenteric occlusion, splenic infarction, and strangulation of a diaphragmatic hernia. While it may be possible to diagnose spontaneous rupture of the esophagus by careful consideration of the onset, course, and physical findings, definite proof from radiologic and thoracentesis studies is possible and should be used to verify the diagnosis in every case.

Radiologic Aspects

Since the radiologic evidence is most important in substantiating the diagnosis it is usually best to make these studies in the radiology department where more complete, technically better and more rapid work can be done.[2,26] Satisfactory bedside studies can

be made in comatous or moribund patients by the interaesophageal instillation of contrast media through a Levine tube, as suggested by Abbott.[1] The radiologic findings can be either suggestive or pathognomonic of rupture of the esophagus. A recognition of the possible significance of the former is most important for if rupture is suspected its presence can be proved by observing the passage of radio-opaque material from the esophagus into the mediastinal and/or pleural space. The radiologic findings will vary depending on the course taken by the rupture. Usually the earliest finding is mediastinal emphysema characterized by widening of the mediastinum and the presence of air along the fascial planes of the mediastinum and later of the neck and subcutaneous tissues. It frequently can be best seen in the lateral projection, especially of the neck where an increase in the width between the posterior tracheal wall and the anterior surface of the vertebral bodies is sought.[26] Mediastinal emphysema is also seen in the spontaneous mediastinal emphysema and as a rare complication of rupture of either the uterus[74] or of a gastric[90] or duodenal ulcer.[56] Because of this rare association of mediastinal emphysema with perforated duodenal or gastric ulcer all patients with the former should have overexposed upright x-ray films of the upper abdomen made. Although only 70 to 80 per cent of proved cases of ruptured duodenal or gastric ulcer will show subdiaphragmatic air, its absence in the presence of mediastinal emphysema definitely rules out the possibility of a ruptured ulcer as the cause of the mediastinal emphysema. Lynch[51] emphasizes the importance of a retrocardiac air bubble and fluid level frequently present but often overlooked in the upright films taken of the upper abdomen of patients suspected of having ruptured duodenal or gastric ulcers, who ultimately prove to have had spontaneous rupture of the esophagus. These findings in association with mediastinal emphysema, or alone if diaphragmatic hernia can be excluded, are diagnostic of ruptured esophagus. The presence of massive, rapidly increasing hydropneumothorax is most suggestive of spontaneous rupture of the esophagus[7,21,64] although spontaneous hemopneumothorax may present identical clinical and radiologic characteristics.[40] Hydrothorax without air is occasionally seen early as a result of effusion secondary to the intense mediastinitis and is therefore associated with the x-ray findings of mediastinitis. If the latter are not recognized the presence of the fluid will at least prevent abdominal surgery and focus attention on the chest as the source of the patients symptoms. The passage of a flexible tube through the rent in the esophagus into the mediastinum as shown by an aberrant position of the tip of the tube on x-ray is not a suggested procedure but its accidental occurrence may be the first clue to

the patient's difficulty and is diagnostic.[33,43] Pneumothorax without demonstrable fluid or with slow accumulation of fluid is so rarely seen with spontaneous rupture of the esophagus that its presence would tend to suggest the diagnosis of spontaneous pneumothorax or spontaneous mediastinal emphysema with secondary pneumothorax. Because of the seriousness of the disorder, the complexity of the differential diagnosis, and the magnitude of the surgical procedures required for its treatment, it would seem valid to insist on absolute verification of the diagnosis of spontaneous rupture of the esophagus by use of radio-opaque media before definitive treatment is begun. This is especially true because the contrast media, either iodized oil[6,85] or barium sulfate suspension[22,33,62] does no apparent harm and will usually be removed immediately at surgery if extravasation occurs.[2,26] Iodized oil is easier to remove from the mediastinal and pleural spaces than barium suspension but there is minimal risk of iodism from its use. In the comatous patient Abbott[1] has successfully used the intraesophageal instillation of iodized oil through a Levine tube passed into the upper esophagus as a bedside procedure.

Thoracentesis

A properly performed thoracentesis in which it can be certain that the tip of the needle is not in a dilated herniated stomach, has not passed through the diaphragm into the stomach, or is not in a blood vessel may give valuable information as well as being of therapeutic value.[4,7,47] If rupture into the pleural space is delayed the pleural effusion which rapidly develops secondary to the mediastinitis will be a typical inflammatory exudate, either sterile or pyogenic.[20] After rupture into the pleural space the aspirated fluid frequently has the characteristic appearance and odor of recently ingested food or liquid.[62,85] It may be colored dirty brown from altered blood but never contains much unchanged blood. This is important for in dissecting anerysm of the aorta with rupture into the pleural space and in spontaneous hemopneumothorax the aspirated fluid is nearly pure blood. The fluid may smell of vomitus or have a sour acrid odor. If it is tested with blue litmus paper or titrated with Topper's solution and sodium hydroxide, it will be found to be strongly acid, proving its gastric origin. Culture of the fluid, though rarely necessary, may reveal massive mixed infection including acidophilus bacillus and other saphrophytes.[85] In a few cases, the diagnosis was suggested by the prompt appearance of some recently ingested colored solution in the pleural cavity or by the appearance of food,[33] colored solution,[62] or massive quantities of fluid through an intercostal drainage tube.[6]

Treatment

The treatment of spontaneous rupture of the esophagus consists of the surgical repair of the rent and/or the drainage of the mediastinal and pleural spaces, and the supportive treatment of the patient. Successful outcome is now possible in these cases because of the advances in thoracic surgery, anesthesiology, antibiotic therapy and blood bank techniques.

There is no single established method of surgical therapy and probably never will be for the surgery will vary with the course taken by the rupture, the status of the esophagus prior to rupture, the interval between rupture and surgery, the presence or absence of high intrapleural and/or intramediastinal pressures, the extraesophageal diseases of the patient and the experiences and limitations of the surgical team. In the usual case with a previously normal esophagus, marked increased intramediastinal pressure and contamination of the pleura, prompt surgical intervention by a transpleural approach with wide drainage of the pleural space after its irrigation and after re-expansion of the lung seems to be the surgical treatment of choice.[6,47,51,80,86] This opinion is based on theoretical, experimental and clinical considerations. Kinsella, Morse and Hertzog[47] in discussing the prognosis of 53 patients reported prior to 1947, emphasize that 25 per cent died in less than 12 hours, 70 per cent in less than 24 hours and 85 per cent in less than 48 hours, and only 15 per cent lived over 48 hours. These figures strongly suggest that immediate definitive therapy is indicated for the majority of patients will not survive long enough to permit delayed or supportive therapy. Ware and Strieder[86] have made careful experimental studies in dogs to study the influence of various types of therapy on survival time. They found no significant difference in the survival time of the control untreated animals and those given only supportive therapy of parenteral fluids, sulfadiazine and penicillin. The animals in whom the same supportive therapy and delayed surgical repair was carried out lived somewhat longer than the first two groups. The majority of those given supportive therapy and prompt surgical repair survived.

Prompt surgical repair of the esophageal rent by a transpleural route has been reported only six times. The patient of Collis, Humphreys and Bond (1944)[20] died within 24 hours of surgery after a technically successful procedure and temporary improvement of the patient. The patient of Kinsella, Morse and Hertzog (1946)[47] seemed well on the road to recovery when he died suddenly on the ninth postoperative day of a massive pulmonary embolus. Barrett's patient (1946),[7] the first to be successfully

managed by direct surgical repair, had a stormy course. Leakage of the esophageal repair occurred on the eighth postoperative day, possibly because of an attack of bronchial asthma. This latter necessitated the drainage of a mediastinal abscess and the establishment of an enterostomy. A complicating lung abscess drained spontaneously through a bronchus yet ultimately a complete cure ensued. Lynch's second patient (1948)[51] also had leakage of the repaired rent on the eighth postoperative day but ultimately had spontaneous closure of the esophageocutaneous fistula and complete recovery. The patient of Olsen and Claggett (1947)[64] and the third patient of Lynch (1948)[51] had relatively smooth postoperative courses, the latter taking a liquid diet on the third postoperative day.

The interval of time between rupture and surgical treatment after which repair of the esophagus would not seem desirable because of likelihood of breakdown of the repair due to inflammation of the esophagus has not been determined. The experiences of Lynch[51] suggest that 24 to 36 hours might be the dividing line. In those patients in whom an attempt to repair the rent does not seem advisable, prompt adequate drainage of the mediastinal and pleural spaces is indicated. In 1938 Benson and Pemberthy[10] reported the first recovery from this disease following closed catheter drainage of the pleural space. Subsequently Graham (1944),[38] Fink (1947),[33] and Moore and Murphy (1948)[62] have reported recovery following closed drainage of the pleural space after rib resection.

The difficulty in adequately draining the mediastinum by these methods and the marked improvement noted by Lynch[51] in patients after wide drainage of the mediastinum suggest that transpleural drainage of the mediastinum into the already contaminated pleural space and subsequent closed drainage of the pleura after re-expansion of the lung should be attempted as soon as possible in these late cases. Lynch (1949)[51] has used this method successfully in one case of spontaneous rupture of the esophagus and Seybold[75] has used it as the treatment of choice in patients with lower esophageal perforation following dilatation of a cardiospasm where the therapeutic problems are similar to those in cases of spontaneous rupture of the esophagus without increased mediastinal pressure.

It would seem wiser to allow the resulting esophageocutaneous fistula to close spontaneously although Moore and Murphy[62] were able to successfully complete an esophagagastroplasty 40 days after rupture and so to markedly shorten the period of hospitalization and medical supervision of the patient. Abbott[1] suggests that in the post-craniotomy patient with spontaneous rupture of the eso-

phagus surgical drainage of the area by intercostal tube or better by rib resection be done initially, and that this be followed at a later date by a definitive plastic repair of the esophagus by resection of the area of esophagomalacia and the reestablishment of continuity by an esophagogastro-anastomosis.

Posterior mediastinotomy with drainage of the mediastinum is indicated in the rare case in which the process is localized in the mediastinum. Gardner (1949)[34] reported recovery of such a case. Overholt[23,66] successfully used a right and then left posterior mediastinotomy in a patient first seen 15 days after rupture with bilateral pleural and mediastinal contamination.

The transabdominal repair of the rent after pulling the esophagus down[31] would seem to be inadequate and undesirable. It would seem better to close the abdomen and approach the lesion through the thorax if the diagnosis should be made at the time of laparotomy. Gastrostomy,[3] jejunostomy[33,51,62] and enterostomy[7] have been used as an adjunct in patients in whom early surgical repair was either not attempted or was not successful. The gastrostomy would seem least desirable because of greater danger of regurgitation into the esophagus and out through the rent. In spite of theoretical objections,[20,37] a Levine tube has frequently been successfully used postoperatively,[10,64] thus eliminating the need of enterostomy as an added surgical procedure.

The supportive measures which are important in the care of these patients, regardless of the surgical treatment used, have been outlined by Kinsella, Morse and Hertzog[47] and by Ware and Strieder.[66] Most important is a realization of the importance of immediate reduction of the high intrapleural and/or mediastinal pressures. The former should be decompressed at once by needle aspiration of the pleural cavity followed by intercostal catheter drainage with suction to prevent its recurrence. The value of mediastinal decompression by a simple collar incision and introduction of a finger into the superior mediastinum was apparent in the patient reported by Vander Laan and Maresh,[61] in whom definite but temporary benefit occurred following this procedure even though the spontaneously ruptured esophagus as the underlying cause of the mediastinal emphysema was not recognized or treated. Ware and Strieder[66] and Lynch[51] emphasize the importance of mediastinal decompression in the care of these patients. Other supportive measures include oxygen, preferably by positive pressure mask, parenteral therapy of whole blood, plasma, dextrose and electrolytes, and massive shotgun chemotherapy with parenteral and intrapleural penicillin and dihydrostreptomycin, parenteral sulfonamides if urine output is adequate, and aureomycin by tube or enterostomy. Decompression of the abdomen

should be maintained by suction through a Levine tube or by an enterostomy. Nothing should be given by mouth or by tube for two or three days. Pleural effusion into the uninvolved side as an early complication and hemorrhage, breakdown of the repair, mediastinal and/or lung abscess, pericardial effusion, and pulmonary embolism as late complications should be carefully watched for and treated with appropriate measures.

The value of modern therapeutic procedures is made evident by an analysis of the approximately 100 cases found in the world's literature. Of this number there were only 13 survivors, all reported since 1938, 10 since 1946.

Case 1: G.B.: J.M.H. No. 31561. A 43 year old white male was apparently in excellent health until he awoke from a nap induced by the consumption of a large amount of beer, vomiting coffee ground material. In the next two and one half hours, he had eight episodes of vomiting of blood, a total, as estimated by the patient, of about one pint. Shortly after the onset of vomiting, he developed slight epigastric soreness. While being examined in the emergency room, he was seized with excruciating pain in the upper abdomen and subxyphoid area which radiated through to the back and was not relieved by an opiate. He was unable to lie on his back but remained curled up on his right side.

His past history revealed an asymptomatic hypertension of three years duration with known systolic levels of 190 mm. Hg.; a "moderate" daily intake of alcohol for years. No previous gastrointestinal disturbances; no previous surgery. System review revealed no other complaints.

Physical examination, performed two and one half hours after onset of symptoms showed an obese white male in acute distress, sweating profusely. Temperature 98.6 (oral), pulse 110, respiration 26, blood pressure 120/80. Positive findings were restricted to the epigastrium where there was marked rigidity, tenderness and rebound tenderness. The lower abdomen and rectal examination were normal. Peristalsis was heard only in the lower quadrants. The chest and cardiovascular systems were normal.

Laboratory studies done soon after entry but after the intravenous infusion of glucose in saline had been begun showed a urine with specific gravity of 1.034, a trace of albumin, 3 plus sugar and 3 plus acetone, a sediment containing a few pus cells and a few hyaline casts per high power field. The blood count showed Hgb. 77 per cent (11.8 Gm.), RBC 4,500,000, WBC 5,650, differential neutrophils 91 per cent (segmented forms 85, stab forms 6), lymphocytes 7, monocytes 2. An upright x-ray film of the abdomen was negative for pneumoperitoneum. Kahn negative.

Course: Three hours after entry 800 cc. of bloody beer was aspirated from the stomach and a laparatomy was performed. No evidence of peritonitis, perforation nor abnormality of the gastrointestinal tract was found. He recovered from the anesthetic still complaining of the severe subxyphoid pain which was not relieved by opiates and of dyspnea. A serum amylase was normal (96 units) and the electrocardiogram showed sinus tachycardia of 176, low voltage, slurring of the QRS and poorly deflected T throughout; interpreted as non-specific myocardial impairment with no evidence of coronary thrombosis. Nine hours after surgery, cyanosis and collapse appeared (B.P. 90/60). There was no response to

oxygen and repeated transfusions. At this time, there was marked subcutaneous emphysema over the upper abdomen, anterior chest, neck, face and upper back. There was dullness, diminished breath sounds and rales over the right chest posteriorly. A portable x-ray film of the chest was interpreted as showing right pleural effusion, marked subcutaneous emphysema and probable pneumomediastinum. No surgical treatment was given and the patient died 27½ hours after onset of hematemesis and 24 hours after onset of acute pain.

Autopsy, done immediately after death, revealed a 6 cm. knifelike slit on the right posterolateral wall of the esophagus, beginning 1½ cm. above the cardia. There were four short mucosal tears of the lower esophagus and cardia but no open vessels were noted. The mediastinum was pocketed with air and green bile-stained fluid. Necrotic food particles were found as high as the arch of the aorta. There was free communication of the mediastinum with the right pleural space which contained similar bile-stained necrotic material. The left pleural space contained a small amount of cloudy exudate and fibrinous pleuritis. Microscopic sections of the esophagus showed only inflammatory changes consistent with an acute process of short duration. Additional findings included marked fatty infiltration of the liver and moderate fatty infiltration of the slightly hypertrophied heart.

Comment: This case represents the rare variation of the Mallory-Weiss[55,89] syndrome in which perforation of the esophagus rather than fatal hematemesis was the mode of death. Except for the hematemesis, which was greater than that usually seen in spontaneous rupture of the esophagus, the entire picture was characteristic of that group of cases in which rupture of a presumably normal esophagus occurs as a result of sudden increased intraesophageal pressure.

Case 2: H.B.: J.M.H. No. 49944. A 68 year old white male was brought in by the police because of moderately severe substernal pain of several hours duration. He was confused and disoriented and remained so until his death 10 days later. The only history available was that he had had some angina pectoris for two years, more severe in the last four months. He had had intermittent ankle edema for several years. Seven months before he had had granted a government pension for heart trouble. The present chest pain had begun several hours before entry, was substernal without radiation, and unassociated with other symptoms.

Physical examination on entry revealed an elderly obese, dirty white male who was lethargic, confused and disoriented but in no distress. Temperature 100 (oral), pulse 90, respiration 18, blood pressure 130/80. The fundi showed moderate arteriosclerosis. Heart enlarged 2 cm. outside the midclavicular line, rate 90, occasional dropped beat. No murmurs or friction rub. Chest clear except for inconstant coarse bilateral basal rales. Abdomen and neurological examination normal except for the mental status.

Laboratory studies on entry revealed the urine to have 4 plus albumin, 7 to 8 red blood cells per high power field in the centrifuged sediment. The blood count: Hemoglobin 85 per cent (13.0 Gm.), RBC 4,300,000, WBC 5,600, Differential—neutrophils 64 per cent (segmented forms 61, stab forms 3), lymphocytes 33 per cent, and monocytes 3 per cent. N.P.N. 48 mgs. per cent. Prothrombin time undiluted 17.2 seconds. Sedimentation rate (corrected Wintrobe) 26 mm. Total serum protein 6.04 Gm., albumin 3.45 Gm., globulin 2.59 Gm. Kahn negative. X-ray film of the chest (Fig.

2a) was interpreted as showing increased markings in both lower lobes but no actual consolidation. An electrocardiogram showed an irregular rate of approximately 130 due to short runs of sinus rhythm with variable A-V response, premature auricular systoles and fusion beats. $T_{1, 2, 3}$ were biphasic. The changes were interpreted as being nonspecific. Lumbar puncture showed the spinal fluid to be clear and colorless under normal pressure but with a positive Pandy reaction and a protein of 113 mgm. per cent. The remainder of the fluid examination was normal.

Course: The patient was digitalized, placed in oxygen, given penicillin parenterally in a dosage of 50,000 units every three hours, and fluid balance was maintained by the oral, then intravenous route. In spite of this therapy, his condition gradually but steadily deteriorated. His temperature ran a septic course with daily elevations to 102-103 degrees (oral), the pulse and respiratory rates increased and the lethargy and confusion increased. The physical findings of the heart, chest, abdomen and nervous system remained as on entry. Serial electrocardiograms showed no change. The NPN dropped to 26 mgm. per cent, the CO2 combining power was 43 Vol. per cent, the urine showed less albumin, no sugar and a few casts. A blood count done on the ninth day of his illness showed Hgb. of 64 per cent (9.9 Gm.), RBC 3,380,000, WBC 3,250. Differential, neutrophils 78 per cent (segmented 64, stabs 10, juveniles 4), lymphocytes 16 per cent, monocytes 4 per cent, eosinophils 2 per cent. Blood smear revealed the neutrophils to show toxic changes. An x-ray film of the chest (Fig. 2b) taken on the ninth day showed definite widening of the mediastinal shadow but no pleural or pulmonary changes. He died suddenly on the tenth day.

Autopsy done 10 hours after death revealed an extensive gangrenous mediastinitis with extension of the gangrenous process into the adjoining portion of both right and left lower lobes of the lung. The pleural spaces contained no free fluid and an obliterative pleuritis walled off the involved lung areas. A large irregular perforation of the lower one-third of the esophagus communicated freely with the mediastinum. The perforation had rolled edematous edges which showed petechial hemorrhages. It extended upward from just above the cardia on the posterior

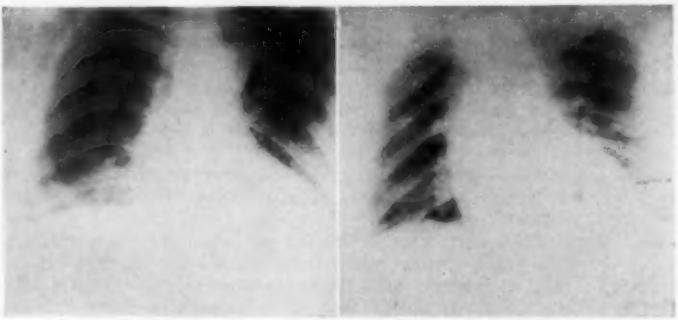


FIGURE 2a FIGURE 2b

Figure 2a: Admission chest film shows only accentuated basal markings.—*Figure 2b:* Ninth day chest film shows marked widening of the mediastinal shadow.

wall. Histological examination of the esophagus showed acute and chronic inflammation and necrosis but no occlusive vascular disease. Grossly the brain was normal but histological examination revealed marked sclerosis of the smaller vessels with multiple small areas of softening throughout the cortical substance. Additional findings included arteriolar nephrosclerosis, coronary sclerosis with myocardial fibrosis and fatty infiltration of the liver.

Comment: This case represents an example of spontaneous rupture due to esophagomalacia secondary to cerebral arteriosclerosis. The correct antemortem diagnosis might have been made had the significance of the progressive widening of the mediastinal shadow been appreciated.

SUMMARY

1) Spontaneous rupture of the esophagus is due to an increase in intraesophageal pressure greater than the tensile strength of the esophagus. Increased intraesophageal pressure is due to the transmission of increased intraabdominal pressure by the stomach contents through the cardia into the esophagus. Rupture is made more likely by distention of the stomach with food or fluid and by obstruction of the espohagus. Obstruction is usually physiological, produced by the complex anatomical makeup of the esophagus and by incoordination of the complex vomiting reflex. Esophagitis, simple ulcer of the esophagus and esophagomalacia weaken the esophagus and so predispose to rupture.

2) Rupture is seen chiefly in association with vomiting and/or retching, alcoholism and diseases of the central nervous system.

3) The linear tear is in the lower third of the esophagus and leads to the rapid development of mediastinitis and/or hydropneumothorax. The 70 per cent mortality in the first 24 hours is due to the violence of the mediastinitis and pleuritis and to the interference with cardio-respiratory function from mechanical compression.

4) In the usual case, a middle aged male, chronic alcoholic, frequently with chronic dyspepsia, during vomiting and/or retching after recent overindulgence in food or alcohol had sudden onset of chest pain, collapse, respiratory distress, upper abdominal rigidity and later subcutaneous emphysema. In the post craniotomy patients vomiting of blood during recovery from anesthesia occurs; consciousness is lost; and there is progressive restlessness, cyanosis, dyspnea with increasing temperature, pulse and respiratory rates.

5) Definite diagnosis is possible by radiologically observing the passage of radio-opaque media through the rent into the mediastinal and pleural spaces or by aspiration of stomach contents from the pleural space. Mediastinal emphysema, rapidly accumulating

hydrothorax, and a retrocardiac air bubble and fluid level are suggestive radiologic findings.

6) In the early cases prompt transpleural repair of the rent is the treatment of choice. In the remainder drainage of the mediastinal and pleural spaces is indicated. The most important of the supportive measures are the decompression of any tension pneumothorax or high pressure mediastinal emphysema, and the use of antibiotic therapy. The various surgical procedures used in the 13 survivors are discussed.

7) Two case reports are given.

RESUMEN

1) La ruptura espontanea del esófago es debida a un aumento de la presión intraesofágica mayor que la que puede soportar el esófago.

Este aumento de presión es debido a la transmisión de presión intrabdominal por intermedio del contenido gástrico hacia el cardias y el esófago. Es más posible que haya ruptura cuando hay distensión del estómago con alimentos o liquidos y por obstrucción del esófago. La obstrucción es generalmente fisiológica, producida por el arreglo anatómico complejo del esófago y por incordinación del reflejo complicado del vómito. La esofagitis, la úlcera simple del esófago y la esofagomalacia debilitan el esófago y así predisponen a la ruptura.

2) La ruptura se ve principalmente en asociación con vómitos o eructos, alcoholismo y enfermedades del sistema nêrvioso central.

3) La desgarradura lineal es en el tercio inferior del esófago y conduce al rápido desarrollo de mediatinitis o hidroneumotórax.

La mortalidad de 70 por ciento que se ve en las primeras 24 horas se debe a la violencia de la mediastinitis y pleiritis y a la interferencia con la función cardio-respiratoria que resulta de la compresión.

4) En el caso habitual se trata de un hombre en edad media de la vida, alcohólico crónico con dispepsia crónica a menudo, que durante el vómito o regurgitación después de haber comido en exceso o bebido mucho alcohol tiene de pronto un dolor en el pecho, colapso, dificultad para respirar, rigidez de la parte superior del abdomen y después enfisema subcutáneo. En los enfermos después de craniotomía, que comitan durante la salida de la anestesia, se pierde la conciencia y hay inquietud creciente, sudores, cianosis, disnea y elevación progresiva de la temperatura, aceleración del pulso y de la respiración.

5) El diagnóstico definido es posible mediante la ingestión de líquido radiopaco que pasa através de la ruptura hacia el mediastino y el espacio pleural. El enfisema mediastínico, hidrotórax que

se acumula rapidamente y burbuja retrocardiaca y nivel liquido son sugestivos radiológicamente.

6) En los casos vistos a tiempo, la reparación por vía transpleural de la ruptura es el mejor tratamiento. En los demás el drenaje de las cavidades mediastinal y pleural están indicados. La medida más importante como auxiliar es la descompresión de cualquier neumotórax a tensión y de cualquier enfisema a alta presión y el uso de antibióticos. Se discuten los diversos procedimientos quirórgicos usados en 13 supervivientes.

7) Se relatan dos casos.

RESUME

1) La rupture spontanée de l'oesophage est due à l'accroissement de la pression intra-oesophagienne, plus grande que la force de tension de l'oesophage. L'accroissement de la pression intraoesophagienne est due à la transmission d'un accroissement de la pression intra-abdominale par l'intermédiaire du contenu gastrique par le cardia dans l'oesophage. La rupture survient plus souvent par la distention de l'estomac avec des aliments ou des liquides, et par l'obstruction de l'oesophage. L'obstruction est habituellement physiologique, produite par la disposition anatomique complexe de l'oesophage et par l'incoordination du réflexe nauséeux. L'oesophagite, l'ulcère simple de l'oesophage et l'oesophagomalacie affaiblissent l'oesophage et le prédisposent à la rupture.

2) La rupture se voit principalement en association avec les vomissements et l'éructation, l'alcoolisme, et les atteintes du système nerveux central.

3) La déchirure linéaire dans la troisième partie inférieure de l'oesophage, conduit au rapide développement d'une médiastinite ou d'un hydropneumothorax. La mortalité de 70% dans les 24 heures est due à la gravité de la médiastinite et de la pleurésie, et au trouble de la fonction cardio-respiratoire qui résulte de la compression mécanique.

4) Dans le cas habituel, un individu moyennant âgé, alcoolique chronique, souvent avec dyspepsie chronique, ressent à l'occasion de vomissements ou d'éructations survenant après un excès de nouriture ou d'alcool, une douleur dans la poitrine. Il présente une tendance au collapsus et on constate une gêne respiratoire, et une rigidité de la partie supérieure de l'abdomen et ensuite de l'emphysème sous-cutané. Chez les malades traités par craniotomie, un vomissement de sang survient pendant le réveil qui suit l'anesthésie; il y a parte de conscience et agitation croissante, cyanose, dyspnée, avec élévation de la température, accélération du pouls et de la respiration.

5) Un diagnostic précis est possible en observant radiologique-

ment le passage du liquide radio-opaque par la rupture dans les espaces médiastinal et pleural, ou par l'aspiration de contenu gastrique dans l'espace pleural. L'emphysème médiastinal, l'hydrothorax s'accumulant rapidement, une bulle d'air rétro-cardiaque et le niveau liquide sont des constatations radiologiques suggestives.

6) Dans les cas précoces, la réparation par voie transpleurale de la rupture est le meilleur traitement. Ensuite le drainage des espaces médiastinal et pleural est indiqué. La plus importante des mesures accessoires est la décompression de la tension du pneumothorax, ou de l'emphysème médiastinal à haute pression, et l'emploi de la thérapeutique antibiotique. L'auteur discute les différents procédés chirurgicaux employés chez les individus qui ont survécu.

7) L'auteur rapporte deux cas.

REFERENCES

1 Abbott, O.: Quoted by Fincher, E. F. and Swanson, H. S.[29]
2 Adams, R.: "Acute Suppurative Mediastinitis," *J. Thorac. Surg.*, 15: 336, 1946.
3 Adams, W.: "Spontaneous Rupture of the Esophagus," *Tr. Path. Soc. London*, 29:113, 1878.
4 Aldrich, C. A. and Anspach, W. E.: "Rupture of the Esophagus from a Blow on the Abdomen," *Radiol.*, 32:93, 1939.
5 Babcock, W. W.: "Textbook of Surgery," 2nd Ed., Philadelphia, *Saunders*, 1935, P. 812.
6 Barrett, R. N.: "Spontaneous Perforation of the Esophagus. Review of the Literature and Report of Three New Cases," *Thorax*, 1:48, 1946.
7 Barrett, R. N.: "Report of a Case of Spontaneous Perforation of the Esophagus Successfully Treated by Operation," *Brit. J. Surg.*, 35:216, 1947.
8 Bartels, E. C.: "Acute Ulcerative Esophagitis. A Pathologic and Clinical Study of 82 Cases Observed at Necropsy," *Arch. Path.*, 20:369, 1935.
9 Beattie, J.: "The Relation of the Tuber Cinereum to Gastric and Cardiac Functions," *Canada M. A. J.*, 26:278, 1932.
10 Benson, C. and Pemberthy, G. C.: "Rupture of the Esophagus in a Child Two Years of Age, With Recovery," *Surg.*, 4:777, 1938.
11 Best, C. H. and Taylor, N. B.: "The Physiological Basis of Medical Practice," Baltimore, *Williams and Wilkins*, 1945, Pp. 490-495.
12 Blackfan, K. D.: Quoted by Cushing H.[24]
13 Bloch, L.: "Acute Ulcerative Esophagitis," *Am. J. Dig. Dis.*, 7:407, 1940.
14 Bockus, H. L.: "Gastroenterology," Philadelphia, *Saunders*, 1944, Vol. I, Sec. 2, Pp. 78-168.
15 Boerhaave, H.: "Atrocis, Nec Descripti Prius, Morbi Historia Secundem Artis Leges," *Conscripta, Ludg. Batav.*, 1724. (Translated by Fitz[30] and McKenzie[57]).
16 Bowles, R. L. and Turner, G. R.: "Rupture of the Esophagus Caused by Vomiting," *Brit. M. J.*, 1:763, 1900; *Lancet*, 1:930, 1900.
17 Boyd, S.: Discussion of Bowles, R. L.[16]
18 Brosch, A.: "Die Spontane Ruptur der Speiserohre auf Greund Neuer Untersuchungen," *Arch. of Path. Anat.* (Virchow's), 162:114, 1900.
19 Burt, C. A. V.: "Pneumatic Rupture of the Intestinal Canal," *Arch. Surg.*, 22:875, 1931.
20 Collis, J. L., Humphreys, D. R. and Bond, W.H.: "Spontaneous Rupture of the Esophagus," *Lancet*, 2:179, 1944.
21 Culver, G. J. and Clark, S. B.: "The Radiographic Diagnosis of Perforations of the Upper Gastrointestinal Tract into the Mediastinum and Pleural Cavity," *Surgery*, 22:458, 1947.
22 Cummings, G. O.: "One Hundred Cases of Esophageal Diseases," *J. Maine M. A.*, 37:275, 1946.

23 Cunningham's Textbook of Anatomy Edited by A. Robinson, New York, *William Wood*, 1931, Pp. 1144-1147.
24 Cushing, H.: "Peptic Ulcer and the Interbrain," *S.G.O.*, 55:1, 1932.
25 Cushing, H.: "Similarity in Response to Posterior Lobe Extract (Pituitrin) and to Pilocarpine when Injected into Cerebral Ventricles," *Proc. Nat. Acad. Sci.*, 17:171, 1931.
26 Dorsey, J. M.: "Surgical Treatment of Perforation of the Esophagus," *Arch. Surg.*, 56:24, 1948.
27 Duval: Cited by Kinsella, T. J., Morse, R. W. and Hertzog, A. J.[47]
28 Eliason, E. L. and Welty, R. F.: "Spontaneous Rupture of the Esophagus," *S.G.O.*, 83:234, 1946.
29 Fincher, E. F. and Swanson, H. S.: "Esophageal Rupture Complicating Craniotomy-Symptom Complex and Proposed Surgical Treatment," *Ann. Surg.*, 129:619, 1949.
30 Fitz, R. H.: "Rupture of the Healthy Esophagus," *Am. J. Med. Sc.*, 73: 17, 1877.
31 Foggett, K. D.: "A Case of Spontaneous Perforation of the Esophagus," *Brit. J. Tuberc.*, 40:133, 1946.
32 Friedenwold, J., Feldman, M. and Zeim, W. F.: "Peptic Ulcer of the Esophagus," *Am. J. Med. Sc.*, 177:1, 1929.
33 Frink, N. W.: "Spontaneous Rupture of the Esophagus, Report of a Case with Recovery," *J. Thoracic Surg.*, 16:291, 1947.
34 Garner, C. McG.: "'Spontaneous' Rupture of the Esophagus," *Arch. Surg.*, 59:710, 1949.
35 Girard, J.: "LaRupture Spontanee de L'Oesophage," *Gaz. d. hop.*, 107: 1117, 1934.
36 Glass, W. E. and Freeman, Wm.: "Spontaneous Rupture of the Esophagus in Syphilis," *Am. J. Med. Sc.*, 189:80, 1935.
37 Gott, R. Jr.: "Spontaneous Rupture of the Esophagus with a Report of Four Cases," *Am. J. Med. Sc.*, 186:400, 1933.
38 Graham, E. A.: "Year Book of General Surgery," Chicago, *Year Book Publishers*, 1944, P. 382.
39 Griffith, R. S.: "Spontaneous Rupture of Esophagus," *Penn. M. J.*, 35: 639, 1932.
40 Hansen, J. L.: "Spontaneous Pneumohemothorax," *Acta. Med. Scand.*, 132:517, 1949.
41 Hatcher, R. A.: "The Mechanism of Vomiting," *Physiol. Rev.*, 4:479, 1924.
42 Hertzog, A. J. and Leighton, R.: "Spontaneous Perforation of Esophagus," *Minn. Med.*, 29:442, 1946.
43 Higginson, J. F. and Clagett, O. T.: "Complete Disruption of the Esophagus, Report of a Case," *J. Thoracic Surg.*, 17:846, 1948.
44 Hoff, E. C. and Sheehan, D.: "Experimental Gastric Erosions Following Hypothalamic Lesions in Monkeys," *Am. J. Path.*, 11:789, 1935.
45 Hoffman, C.: "Ueber die Erweichung und den Durchbruch der Speiseroehre und des Magens," *Arch. Path. Anat.*, 44:352, 1868.
46 Jackson, C.: "Peptic Ulcer of the Esophagus," *J.A.M.A.*, 92:369, 1929.
47 Kinsella, T. J., Morse, R. W. and Hertzog, A. J.: "Spontaneous Rupture of the Esophagus," *J. Thoracic Surg.*, 17:613, 1948.
48 Klein, L. and Grossman, M.: "Rupture of the Esophagus," *M. Bull. Vet. Admin.*, 19:277, 1943.
49 Kyle, J. T.: "Spontaneous Rupture of Oesophagus," *Brit. M. J.*, 1:977, 1935.
50 Light, R. U., Bishop, C. C. and Kendall, L. G.: "The Production of Gastric Lesions in Rabbits by Injection of Small Amounts of Pilocarpine into the Cerebrospinal Fluid," *J. Pharm. and Exp. Ther.*, 45:227, 1932.
51 Lynch, J. P.: "Spontaneous Perforation of the Esophagus," *N. E. J. Med.*, 241:395, 1949.
52 Mallam, P. C., Whiteloche, H. A. B. and Robb Smith, A. H. T.: "Spontaneous Rupture of Esophagus," *Brit. J. Surg.*, 27:794, 1940.
53 Mallory, G. K. and Weiss, S.: "Hemorrhages from Lacerations of the Cardiac Orifice of the Stomach due to Vomiting," *Am. J. Med. Sc.*, 178:506, 1929.
54 Mallory, T. B.: "Case Records of the Massachusetts General Hospital," *N. E. J. Med.*, 222:230, 1940.
55 Masten, M. G. and Bunts, R. C.: "Neurogenic Erosions and Perfora-

tions of the Stomach and Esophagus in Cerebral Lesions," *Arch. Int. Med.*, 54:816, 1934.
56 McCurkle, H. and Stevenson, J.: "Subcutaneous Emphysema Associated with Perforated Gastric Ulcer," *Surgery*, 2:930, 1937.
57 McKenzie, M.: "Diseases of the Nose and Throat," Philadelphia, *P. Blakiston*, 1934, Vol. 2, Sect. 4, Pp. 17-235.
58 McWeeney, E. J.: "On Rupture of the Apparently Healthy Oesophagus," *Lancet*, 2:158, 1900.
59 Menne, F. R. and Moore, C. U.: "Spontaneous Rupture of Esophagus in an Infant," *Arch. Pediat.*, 38:672, 1921.
60 Meyer, J.: Cited by Walker, I. J.[84]
61 Miller, G. I.: "Unexplained Perforation of the Esophagus in a Girl Ten Years Old," *Post. Grad. M. J.*, 26:312, 1911.
62 Moore, J. A. and Murphy, J. D.: "Spontaneous Rupture of the Esophagus," *J. Thoracic Surg.*, 17:632, 1948.
63 Murdock, J. R.: "A Case of Rupture of the Oesophagus by Indirect Violence," *Lancet*, 2:1292, 1928.
64 Olsen, A. M. and Clagett, O. J.: "Spontaneous Rupture of the Esophagus, Report of a Case with Immediate Diagnosis and Successful Surgical Repair," *Post. Grad. Med.*, 2:417, 1947.
65 Opper, L. and Zimmerman, H. M.: "Ulcers of the Digestive Tract in Association with Cerebral Lesions," *Yale J. Biol. and Med.*, 11:49, 1938-1939.
66 Overholt, R.: Personal communication, 1949.
67 Pavy, F. W.: "Treatise on the Function of Digestion. Its Disorders and Their Treatment," Philadelphia, *Lea*, 1869, Pp. 88-105.
68 Penner, A. D. and Bernheim, A. I.: "Acute Postoperative Esophageal, Gastric and Duodenal Ulcerations," *Arch. Path.*, 28:129, 1939.
69 Rankin, L. M.: "Perforated Ulcer of Esophagus Following a Burn," *Am. J. Surg.*, 67:134, 1945.
70 Ridgeway, E. C. Jr. and Duncan, G. G.: "Spontaneous Rupture of the Esophagus. Review of Literature and Report of One Case," *Bull. Ayer. Clin. Lab., Penn. Hosp.*, 3:79, 1937.
71 Robson, L. C.: "Perforated Esophagus Following Burns," *Brit. M. J.*, 1:414, 1943.
72 von Rokitansky, C. F.: "Pathological Anatomy," London, *The Sydenham Soc.*, 1849, Vol. 2, Pp. 35-39.
73 Roy, D. W. and Contab, B. C.: "A Case of Ruptured Oesophagus," *Lancet*, 2:1765, 1911.
74 Ryssing, E.: "Rupture of the Uterus with Extraperitoneal, Mediastinal and Subcutaneous Emphysema," *Acta. Obst. Gynec. Scand.*, 28:86, 1948.
75 Seybold, W. D.: Personal communication, 1949.
76 Sheldon, L.: "Report of a Death from Rupture of the Esophagus," *U. S. Navy M. Bull.*, 13:529, 1919.
77 Smead, L. F.: "Spontaneous Rupture of the Esophagus Following Vomiting," *Am. J. Surg.*, 13:497, 1931.
78 Terrocal, J.: "Les Maladies d L'Oesophage," Paris, *Mason*, 1938, Pp. 360-362.
79 Tileston, W.: "Peptic Ulcer of the Oesophagus," *Am. J. Med. Sci.*, 132: 240, 1906.
80 Turner, G. G.: "Injuries and Diseases of the Oesophagus," London, *Cassell and Co.*, 1946, 1st Ed., Pp. 46-50.
81 Vander Laan, W. P. and Maresh, G.: "The Significance of Mediastinal Emphysema," *N. E. J. Med.*, 235:617, 1946.
82 Vinson, P. P. and Butt, H. R.: "Esophagitis, A Clinical Study," *J.A. M.A.*, 106:994, 1936.
83 Vinson, P. P.: "The Diagnosis and Treatment of Diseases of the Esophagus," Springfield, Ill., *Charles C. Thomas*, 1940, Pp. 46-61, 170-177.
84 Walker, I. J.: "Spontaneous Rupture of the Healthy Esophagus," *J.A. M.A.*, 62:1952, 1914.
85 Wallfield, M. J.: "Pleural Manifestations of Perforation of the Esophagus," *Am. J. Dis. Child.*, 58:1261, 1939.
86 Ware, P. F. and Strieder, J. W.: "Spontaneous Perforation of the Normal Esophagus," *Dis. Chest*, 16:49, 1949.
87 Watts, J. W. and Fulton, J. F.: "The Effect of Lesions of the Hypothalamus Upon the Gastrointestinal Tract and Heart in Monkeys," *Ann. Surg.*, 101:363, 1935.

88 Weder, A.: "Spontanruptur der Speiderohre," *Acta. Oto-Laryngologica*, 31:426, 1943.
89 Weiss, S. and Mallory, G. K.: "Lesions of the Cardiac Orifice of the Stomach Produced by Vomiting," *J.A.M.A.*, 98:1353, 1932.
90 Welty, D. M.: "Mediastinal Emphysema Following Anterior Perforation of a Gastric Ulcer," *Ann. Int. Med.*, 30:205, 1949.
91 Whipham, T. R. C.: "A Case of Rupture of the Esophagus from an Accident," *Lancet*, 2:749, 1903.
92 Eggers, C. and Maier, H. C.: "The Esophagus." In "Nelson's Loose Leaf Surgery," *Whipple, Allen O.*, Vol. 4, P. 130.
93 Williams, T. H. and Boyd, Wm.: "Spontaneous Rupture of the Oesophagus," *S. G. O.*, 42:57, 1926.
94 Zenker, F. A. and Ziemssen, H.: "Diseases of the Esophagus." In "Cyclopaedia of Medicine," New York, *Wm. Wood*, 1878, Vol. 8, Pp. 89–104.
95 Zohman, B. L.: "Peptic Ulcer of the Esophagus," *Med. Jour. and Rec.*, 198:86, 1933.

For additional references see Barrett, R. N.,[6] Kinsella, T. J., Morse, R. W. and Hertzog, A. J.,[47] and Weder, A.[88]

Diffuse Bilateral Fibrocystic Disease of Lungs (Honey-Comb Lungs)*

LEROY HYDE, M.D., F.C.C.P., BERNARD HYDE, M.D., F.C.C.P.
and CHARLES POKORNY, M.D.
Los Angeles, California

"Anatomic studies indicate that this (congenital cystic disease) is an extremely rare condition; it has not been found at necropsy in the Babies Hospital during a period of 50 years. Schenck quotes Lederer as having failed to find a single instance of congenital cystic disease in 5,000 necropsies. It is now evident that many cases which have suggested congenital cysts roentgenographically were probably examples of acquired emphysematous cavities caused by check-valvular bronchial obstruction."[1]

Two cases proved at autopsy and two patients now living and well are presented as examples of diffuse bilateral fibrocystic disease of the lungs.

Case Reports

Case 1: S.P. This 36 year old white male was admitted to Birmingham Veterans Hospital on March 3, 1948, with a history of progressive shortness of breath and cyanosis on exertion for the previous two and one half years. A chest roentgenogram taken in April 1945, on admission to the Army was normal (Figure 1). The patient was perfectly well until August 1945, when he "passed out." He was admitted to a hospital with the diagnosis of "meningitis" which was later changed to "influenza." Ten days later, he was discharged back to duty, but he noted persistent weakness, cough, and a slight amount of green sputum. He found that he could no longer keep up with the training program and also noticed the development of numbness of the hands and feet worse with exercise. On return to civil life, he worked as a truck driver. He was forced to discontinue this because of weakness and fatigue. In 1946, he noticed cyanosis on exposure to cold air which has increased in intensity to the present time. Hospitalization in 1946 revealed peripheral vascular disease, compatible with thromboangiitis obliterans. When examined in 1948, he was well developed and fairly well nourished. There was peripheral cyanosis and marked shortness of breath on mild exertion. The anterior-posterior diameter of the chest was increased. Percussion was hyperresonant bilaterally. Bronchial breathing was noted over the entire chest. The heart was negative except for accentuation of the pulmonic second

*From the Pulmonary Diseases Service, Birmingham Veterans Administration Hospital, Van Nuys, California, and the College of Medical Evangelists, and The White Memorial Hospital, Los Angeles, California.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration

sound. The red blood count was 4.6 million cells per cubic millimeter with 17.25 grams of hemoglobin per 100 cubic centimeters of blood. The differential count was normal. Urinalyses were normal. All sputa for acid fast bacilli and fungi were negative. The serum albumin was 4.2 grams per cent and the serum globulin was 2.1 grams per cent. Electrocardiograms revealed right heart prominence and right heart strain. Coccidioidin skin test and tuberculin P.P.D. strengths 1 and 2 were negative. The venous pressure was 130 mms. of water. The vital capacity was 2.2 liters. Circulation times using flurescein were: arm to arm 19.4 seconds; arm to foot 66.2 seconds; arterial segment time 46.8 seconds. Chest roentgenograms (Figures 2 and 3) revealed diffuse bilateral fibrocystic disease. The patient failed to respond to numerous medications. He became progressively worse with increased dyspnea and cyanosis and expired on June 9, 1948.

At autopsy (Drs. B. E. Konwaler, A. Lack, C. S. Stitts), the heart was found to weigh 400 grams. The right chambers were moderately dilated. The wall of the right ventricle measured 9 mms. and that of the left ventricle 11 mms. The valves had the following measurement: mitral 95 mms., aortic 80 mms., pulmonic 85 mms., and tricuspid 130 mms. The myocardium had a red-brown tinge and was not remarkable. Coronary arteries were patent and appeared normal. The aorta was smooth and glistening. Microscopically there was marked thickening of the myocardial fibers of the right ventricle with barrel-shaped nuclei. Numerous areas of perivascular fibrosis with lymphocytic infiltration were noted. There was generalized hyperemia with interstitial lymphocytic infiltration. Coronary arteries and pericardium were normal.

Both lungs were markedly emphysematous and presented innumerable bleb-like projections from the surfaces (Figure 4). The blebs measured from one to two millimeters in diameter, and had a pearly grey

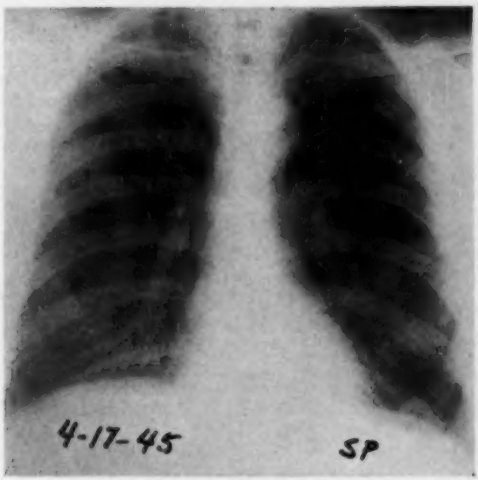


FIGURE 1, Case 1, S.P.:
Chest roentgenogram, April 17, 1945, is normal.

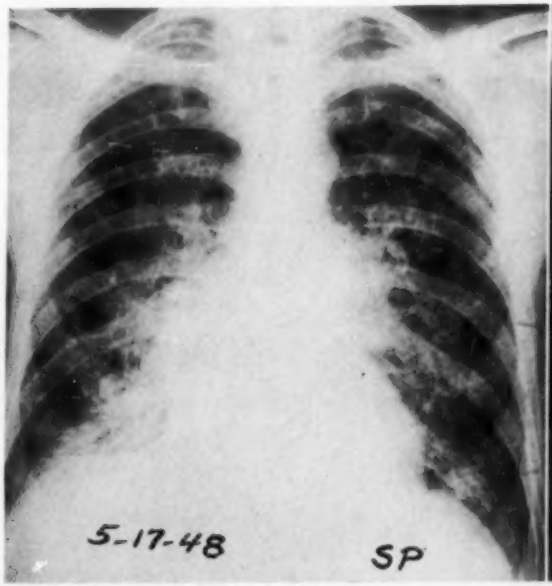


FIGURE 2

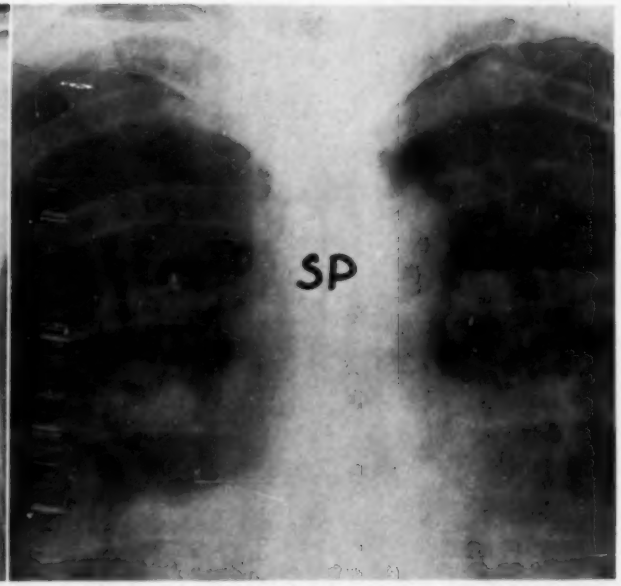


FIGURE 3

Figure 2, Case 1, S.P.: Roentgenogram May 17, 1948, reveals bilateral fibrocystic disease.—*Figure 3, Case 1:* Enlargement of Fig. 2.

appearance. The right lung weighed 900 and the left 700 grams. Scattered between the blebs were seen purplish-red areas of apparently normal lung tissue. On cut section, both lungs were seen to contain throughout many cyst-like areas, some of which communicated with bronchioles. The cysts measured from one to two millimeters in diameter. An increase in fibrous tissue was seen toward the hilum of the lung. The lungs were relatively dry. Pleura was normal. Microscopically (Figure 5), many small cysts lined by several layers of flattened epithelium were noted. The interstitial tissue surrounding these cysts showed a marked increase in fibrous tissue with infiltration of many lymphocytes and some plasma cells. Some of the cysts contained clear mucoid-like substance with a few macrophages. However, for the most part the cysts were free of debris. In several areas there were irregular infoldings of the wall of the cysts with almost complete obliteration of the lumen giving the appearance of fibro-adenomatous tissue, characteristic of congenital cystic disease. In a few areas the cysts communicated with an adjoining bronchiole, but most of them appeared to be independent. In the pulmonary tissue not involved by the cyst-like areas, there were numerous areas of emphysema and atelectasis. Many of the alveolar walls showed marked congestion. The alveolar spaces in some areas contained red blood cells, white blood cells and macrophages with hemosiderin. Most bronchioles were clear, and contained no debris. The arterioles showed marked congestion. Their intimae disclosed rather marked thickening with an increase in the fibrous tissue surrounding the arterioles. Chronic passive congestion of the liver, kidneys, spleen, and gastro-intestinal tract and hyperplasia and congestion of the peritracheal lymph nodes were also poted.

Case 2: J.S.G. This 36 year old white salesman gave a history of being perfectly well until after entering the Army in 1943. A chest roentgenogram in March 1943 was entirely normal. A chest roentgenogram in November 1943 revealed diffuse bilateral fibrocystic disease. This patient was a pilot, and following an ascent in a pressure chamber, developed cough, shortness of breath, and fatigue in the fall of 1943. Since that time, his symptoms became progressively worse. He was discharged from the Army in July 1945, with the diagnosis of pulmonary fibrosis.

The patient was first seen by us on August 30, 1948, stating that approximately 30 days previously he had developed sudden right chest pain which increased his dyspnea and cough.

Examination of the chest revealed expansion to be limited bilaterally. There was hyper-resonance over the right chest with absent breath sounds, and hyper-resonance over the left chest with diminished breath sounds. A chest roentgenogram at that time revealed right pneumothorax of approximately 40 per cent. The roentgenographic diagnosis was chronic intestitial fibrosis with cystic changes and spontaneous right pneumothorax. The patient refused hospitalization. He died suddenly four months later. An autopsy was performed as a coroner's case, by Dr. Cecil F. Baisinger, who placed his slides at our disposal. The lungs were heavier than normal; the left weighed 860 and the right 740 grams. Surfaces were irregular with numerous slightly elevated areas measuring from a few mms. to the largest which measured 1 cm. across. The pleura was moderately thickened and there were a few bullous air spaces bulging beneath the pleura. Multiple sections through the lobes of both lungs revealed many dilated air sacs with small cysts filled with air. These spaces had a distinct fibrous tissue lining which glistened. In some

areas large spaces were produced by confluence of several air sacs, and fibrous cords traversed the cystic spaces. These air cysts measured from 2 to 4 millimeters in most places. The smaller cysts had thin walls and the larger ones thick fibrous walls. The tissue between the cystic areas was fibrous. The islands of lung parenchyma which remained were nearly all less than 1 cm. across. The air cysts connected with the bronchial tree by small bronchioles. The thoracic lymph nodes were rather large and moist.

The heart was markedly enlarged and weighed 580 grams, when empty. The enlargement was due primarily to hypertrophy and dilatation of the right ventricle, the wall of which measured 5 mms. in thickness. The wall of the left ventricle was 16 mms. in thickness. The triscuspid ring was dilated to 15.5 cms. in circumference, the pulmonic was 9.5 cms., the mitral 11 cms., and the aortic 8 cms. The valve leaflets were essentially normal. The coronary arteries showed no significant sclerosis. The aorta was elastic. The anatomic diagnoses were fibro-cystic disease of the lungs, diffuse, bilateral; pneumothorax spontaneous, right; and hypertrophy and dilitation of the right heart (cor pulmonale).

Microscopic sections of the lungs (examined by Dr. B. E. Konwaler) showed many cystic spaces occupying the major portion of the lungs. Some of these spaces were lined by a low cuboidal epithelium; others were lined by ciliated columnar type epithelium while in still other areas no definite epithelium could be recognized. In some areas, the cystic spaces were filled with a pink staining granular debris; other spaces were empty. In general, the histologic appearance of these spaces was that of markedly dilated small bronchioles. Between the spaces there were prominent fibrous trabeculae. This fibrosis of the lung extended also to non-cystic areas but was less marked there. Scattered throughout the interstitial tissue were collections of inflammatory cells, mainly lymphocytes. The vascularity of the interstitial tissue was prominent and many of the vessels were dilated and filled with red blood cells. This vascularity and stasis were such as seen in pulmonary hypertension and cor pulmonale. Some of the alveolar spaces were emphysematous while many others

FIGURE 4, Case 1, S.P.: Lung at autopsy. Arrows point to several of the many small cysts.

were filled with edema fluid or contain pigment-filled histiocytes. Occasional areas showed active pneumonitis with collections of polymorphonuclear leucocytes. The sections thus showed not only cystic disease of the lung, but also considerable fibrosis, the latter probably being of greater significance in the production of symptoms of cor pulmonale. The diagnosis was "fibrocystic disease of the lung, with pulmonary edema and pneumonitis."

Case 3: F.B.D. This 29 year old white male's routine chest roentgenogram in October 1945, revealed diffuse bilateral infiltrations. Numerous roentgenograms since then have shown no change. All sputum concentrates and cultures have been negative for acid fast bacilli. The patient had recurrent left spontaneous pneumothoraces in January 1949. He denied all pulmonary symptoms except for rare exertional dyspnea. His weight was 124 pounds. Systemic review was non-contributory.

In May 1949, he did not appear ill. He was 25 pounds underweight. There were signs of left pneumothorax, namely, absent breath sounds over the entire left lung with hyperresonance. The right lung was normal to percussion and auscultation. The systolic blood pressure was 120 mm. and the diastolic 80 mm. Complete blood counts, blood serology and urines were entirely normal. Chest roentgenograms revealed diffuse bilateral fibro-cystic infiltrations. Planigrams revealed a reticular infil-

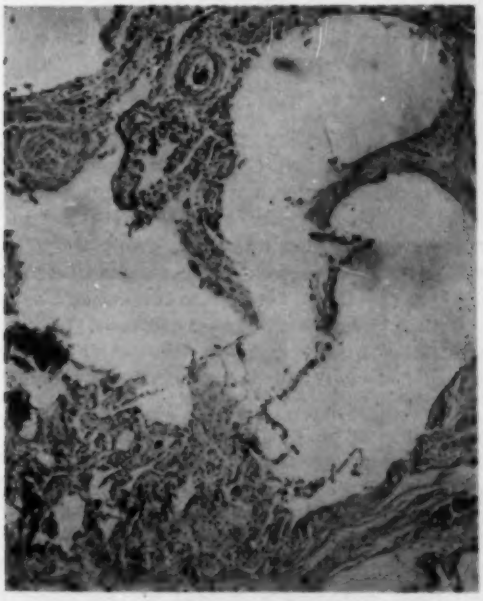


FIGURE 5, Case 1, S.P.: Small pulmonary cysts with increased fibrous tissue in interstitial tissue surrounding the cysts. (x 35).

tration with suggestive cyst-like areas. The patient was entirely afebrile and asymptomatic in the hospital. The left pneumothorax cleared on bedrest and he was discharged. The patient attends school.

Case 4: S.B. This 31 year old white male was afebrile and asymptomatic when first observed. His history revealed mumps, malaria, and homologous serum jaundice four years prior to examination in 1944. Although a chest roentgenogram taken on entrance to the Army in 1941 was negative, a routine chest film taken one year later in the fall of 1942, revealed extensive bilateral fibro-cystic changes. These chest roentgenograms are not available but chest films of 1944 and 1946 are. The patient felt well during the following five years from 1944 to the present, except for an occasional rare morning cough and several bouts of unexplained fever. He is alive and well, on active duty with the United States Air Forces.

Physical examination in 1946 revealed a well developed and well nourished white male who did not appear acutely or chronically ill. The blood pressure was 110 mms. systolic and 60 mms. diastolic. Physical examination was entirely normal. The lungs were clear to percussion and auscultation.

Routine laboratory examinations were within normal limits, including complete blood count, sedimentation rate, blood serology and urine. Both coccidioidin and histoplasmin tests were positive. The serum albumin and globulin were normal. Roentgenograms of the chest revealed numerous fibro-cystic densities throughout both lungs from apex to base. There was no enlargement of the peribronchial or hilar lymph nodes. X-ray films of the hands were negative.

Discussion

Diffuse bilateral fibro-cystic disease of the lungs is relatively rare. Its pathogenesis is not clear. Numerous terms have been applied to this condition, such as polycystic lung and honey-comb lung. Willis and Almeyda[4] have reviewed the literature and have divided cystic pulmonary lesions into two groups: (1) those derived from alveoli, as solitary alveolar cyst, pneumatocele, and cystic emphysema, and (2) those derived from bronchi, as solitary or multiple bronchial cysts or cystic bronchiectasis. Cysts of the lungs manifest at birth or infancy are the result of faulty development and are derived from bronchi and bronchioles and not from the alveoli.[2]

Roentgenographic differentiation of cystic lesions of the lungs may be difficult. It is our impression that the single or several large cysts seen in patients during or past middle age and often with emphysema are examples of alveolar cysts and may be termed cystic emphysema. The lobular or lobar areas of cystic bronchiectasis are no problem, being simply a variation of bronchiectasis.

Diffuse bilateral fibro-cystic disease of the lungs (polycystic lungs or honey-comb lungs), however, appears to be a different entity, occurring in younger patients, usually males, being bila-

teral, and often leading to secondary affects in the lungs and heart (cor pulmonale) with subsequent death. The lesions may be congenital or acquired, with differentiation being practically impossible to make in any given case unless the lesions are discovered soon after birth or in infancy.

The cause of congenital polycystic disease in general is still unknown. Norris and Tyson[2] believe the fundamental lesion to be focal segmentation preceded or followed by focal dilatation of small bronchi and bronchioles. Isolated segments of bronchi may develop into gradually enlarging cysts. Norris and Tyson note that the lesions and sequence of polycystic lung changes are similar to those described in polycystic kidney, liver and pancreas. Oswald and Parkinson[3] in an excellent review of "honey-comb lungs" note 16 cases of cystic disease, with small thin walled cysts distributed uniformly throughout both lungs. Seventeen previously reported cases are also reviewed and classified. In 23 cases, including six of these authors' cases, the diffuse bilateral fibro-cystic pulmon-

TABLE I

Honeycomb Lungs of Uncertain Aetiology[3]

Cases	Sex	Age at onset (years)	Duration to death (years)	RESPIRATORY — — SYMPTOMS — — Spontaneous Pneumothorax	Right heart Failure	Radiological reticulation of lungs
Case 7	F	7	0	++D	—	+
Case 8	M	12	2	++	—	+
Case 9	M	16	10	++	—	0
Case 10	M	18	A	++	—	+
Case 11	M	23	A	++	—	+
Case 12	M	24	A	++	—	+
Case 13	F	25	1	—	+D	+
Case 14	M	26	1	—	+D	+
Case 15	M	53	1	—	+D	+
Case 16	M	55	2	—	+D	+

Other findings:

Case 8: Transient polyuria.

Case 9: Dissecting aneurysm (D), medionecrosis idiopathica cystica of aorta.

Case 12: Sister had spontaneous pneumothorax.

Case 13: Patent foramen ovale, arachnodactyly.

+ = Present. — = Absent. D = Cause of death.
0 = Not recorded. ++ = Bilateral. A = Alive at time of report.

ary lesions were associated with a general medical disease, as xanthomatosis, biliary cirrhosis, tuberous sclerosis, or pituitary disease (four cases of diabetes insipidus, and one pituitary dwarf). In the other 10 cases the diffuse bilateral fibro-cystic pulmonary lesions were an isolated finding and no cause was found.

Table I is taken from Oswald and Parkinson's excellent paper and reviews their "honey-comb lungs" without known cause. (The case numbers of Table I are from their paper). Table II summarizes the present four cases.

As with all developmental defects, treatment is unsatisfactory. Avoidance of bronchopulmonary infections and prompt treatment of these with antibiotics are indicated. The ultimate prognosis is poor.

TABLE II

Present Series

Cases	Sex	Age at onset (years)	Duration to death (years)	RESPIRATORY — — SYMPTOMS — — Spontaneous Pneumothorax	Right heart Failure	Radiological reticulation of lungs
1 (SP)	M	34	2	—	+	+
2 (JSG)	M	31	5	+	+	+
3 (FBD)	M	15	A (4)	++	—	+
4 (SB)	M	27	A (7)	—	—	+

Other findings:

Case 1: Had thromboangeitis obliterans. Negative tuberculin and coccidioidin tests.

Case 3: EKG normal. Asymptomatic.

Case 4: Negative coccidioidin and histoplasmin tests. Tuberculin reactor. Asymptomatic.

+ = Present. ++ = Bilateral. — = Absent.
A = Alive at time of report (Number in parenthesis refers to years following first abnormal x-ray).

SUMMARY AND CONCLUSIONS

1) Four cases are presented as examples of diffuse bilateral fibro-cystic disease of the lungs. Two were proved at autopsy and two are suggestive clinically, but unproved.

2) Diffuse bilateral fibro-cystic disease of the lungs (polycystic disease, honey-comb lung) is quite rare. The entity differs from ordinary cystic emphysema and alveolar cysts.

3) Diffuse bilateral fibro-cystic disease occurs in younger patients, usually males, and often produces secondary effects on the lungs and heart (cor pulmonale) with subsequent death.

4) The fundamental lesion is believed to be focal segmentation preceded or followed by focal dilatation of small bronchi and bronchioles. Isolated bronchial segments may gradually develop into cysts.

5) Treatment is unsatisfactory and the ultimate prognosis is poor.

Grateful acknowledgement is made to Dr. Benjamin E. Konwaler for the pathologic findings of Case 1 and for reviewing the miscroscopic slides of Case 2, to Dr. Cecil F. Baisinger for the summary of the gross pathologic findings and the microscopic slides of Case 2, and to Thomas S. Masterson and E. A. Dagner of the Medical Illustration Department of the Birmingham Veterans Hospital for the photographs.

RESUMEN Y CONCLUSIONES

1) Se presentan 4 casos como ejemplos de la enfermedad fibrocística difusa del pulmón. Dos fueron demostrados a la autopsia y dos fueron sugestivos clínicamente pero no se demostraron.

2) La enfermedad fibrocística difusa bilateral de los pulmones (enfermedad policística, pulmón en panal) es bastante rara.

La afección difiere del ordinario enfisema cístico y de los quistes alveolares.

3) La enfermedad ocurre en personas jóvenes y produce a menudo efectos secundarios en los pulmones y en el corazón (cor pulmonale) con muerte consecutiva.

4) La lesión fundamental se cree que sea la segmentación focal precedida o seguida de dilatación focal de los bronquios pequeños y de los bronquios. Los segmentos bronquiales pueden gradualmente convertirse en quistes.

5) El tratamiento no es satisfactorio y el pronóstico a la larga es malo.

RESUME

L'auteur présente 4 cas de maladie fibro-kystique bilatérale diffuse des poumons. Deux cas ont fait leur preuve par l'autopsie, et les deux autres sont très probables par les examens cliniques, mais n'ont pas été vérifiés.

La maladie fibro-kystique diffuse bilatérale des poumons (maladie polykystique, poumon en nid d'abeilles) est assez rare. Elle est différente de l'emphysème ordinaire kystique et des kystes alvéolaires.

La maladie fibro-kystique bilatérale diffuse atteint les malades jeunes, de sexe masculin généralement, et produit souvent des effets secondaires sur les poumons et le coeur (coeur pulmonaire) avec mort consécutive.

L'auteur croit que la lésion fondamentale est un foyer de seg-

mentation précédé ou suivi d'un foyer de dilatation des petites bronches et des bronchioles. Les segments bronchiques isolés peuvent se développer graduellement en kystes.

Aucun traitement n'est satisfaisant, et le pronostic reste grave.

REFERENCES

1 Caffey, John: "Pediatric X-ray Diagnosis," 1945, *The Year Book Publishers, Inc.*, Chicago, P. 234.
2 Norris, Robert F. and Tyson, Ralph M.: "The Pathogenesis of Congenital Polycystic Lung and Its Correlation with Polycystic Disease of Other Epithelial Orangs," *American Journal of Pathology*, 23:1075, 1947.
3 Oswald, Neville and Parkinson, Thomas: "Honeycomb Lungs," *Quarterly Journal of Medicine*, 18:1, 1949.
4 Willis, F. E. S. and Almeyda, J.: "Cystic Disease of the Lung (Bronchoalveolar Cyst)," *Tubercle*, 24:27 and 43, 1943.

Bronchogenic Carcinoma Masked by Pulmonary Tuberculosis: Case Report

J. R. PHILLIPS, M.D., F.C.C.P. and J. W. MORRISON, M.D.
Houston, Texas

A double disease process is frequently the last possibility to be considered in a confusing diagnostic picture. The natural tendency to explain all findings, symptoms and complaints under a single disease entity, is not without its pitfalls. Then, too, the development of a second disease process, in addition to, and masked by, an older pre-existing process, creates an even greater challenge to the diagnostician.

Pulmonary tuberculosis and bronchogenic carcinoma, because of their common qualities of insidious onset, debilitation of the patient, the production of similar symptoms, such as cough, sputum, hemoptysis, chest pain, etc., and frequent similarity of roentgenograms, are a well-suited duet to masquerade as a single disease. Bronchogenic carcinoma may suddenly begin in a tuberculous lung and progress for some time without detection, especially if the neoplastic lesion tends to mimic or blend into the original tuberculous lesion.

The incidence of coexisting primary lung carcinoma and pulmonary tuberculosis probably occurs more often than is generally believed. Robins and Silverman state that there have been more than 100 reported cases in the American literature alone, since 1932. They add 12 cases in their report and fix the incidence of carcinoma of the lung in cases of tuberculosis at about 1.5 per cent. As Feld and O'Malley have pointed out, the increase in bronchogenic carcinoma in recent years is probably due to better detection through improved diagnostic methods and a better concept of lung tumors, rather than an absolute increase in the incidence of the neoplasm. This may also be true of the incidence of its coexistence with tuberculosis. There appears to be no conclusive evidence to show that tuberculosis predisposes to lung carcinoma, or vice versa.

According to Cooper, earlier workers, notably von Rokitansky, Lubarsch and Pearl, advanced a theory of antagonism between the two diseases; that the presence of one "immunized" the patient against the other. However, this theory was later convincingly disputed by Moak, Carlson and Bell, and Oertel. Cooper concluded that the association of carcinoma and tuberculosis had best be regarded as coincidence in the light of our present knowl-

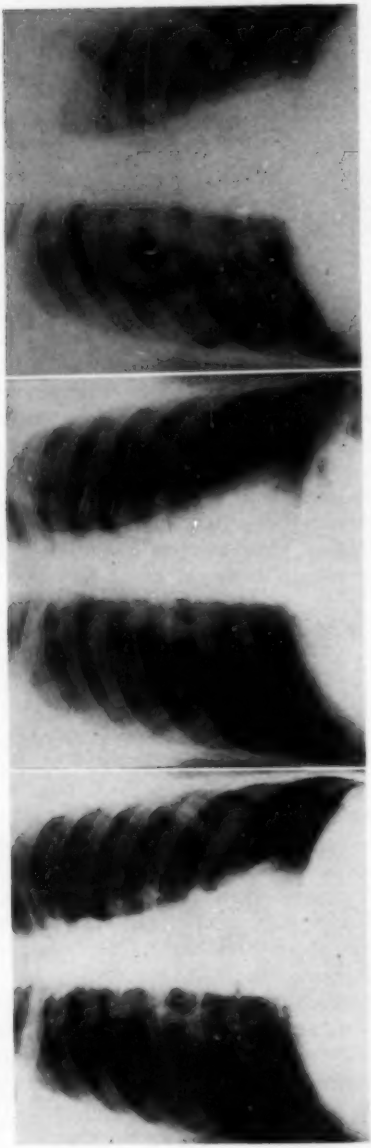


FIGURE 3

FIGURE 2

FIGURE 1

edge of the etiology of malignant neoplasms. This view is the opinion shared by many in the literature (Ross, Edwards, Ritterhoff, Fulton and Rolleston and others).

Case Report

Mr. M. A. L. (Hospital Case No. 5020), a 39 year old white male, entered St. Joseph's Infirmary, July 10, 1949. He complained of persistent cough, production of thick, blood-tinged sputum, sharp pain in his left chest anteriorly, weight loss and marked fatigue.

The history of his trouble dated to early in 1945 when he had consulted a physician in another city, because of a "slight discomfort and flu" in his chest. He had coughed up some blood-tinged sputum at that time. A chest x-ray inspection revealed an infraclacicular lesion in the left upper lobe, compatible with early primary tuberculosis (Fig. 1). He stated that he "seemed to recover" from this illness in a short time and returned to work as a pipe-fitter.

In September of 1947, approximately two years later, he consulted an internist complaining of sharp pain in the anterior chest, over the precordial area, coughing up blood-tinged sputum, and generalized weakness. The pain was steady and did not radiate. On physical examination it was noted that he presented a thin, emaciated appearance. Bronchial breathing and dulness to percussion were present in the left upper chest, and there were some coarse rales over the entire left chest. Aside from these findings, the examination showed nothing of note. An electrocardigram was reported normal and a sputum examination negative for acid-fast bacilli. A complete blood count showed hemoglobin of 120 per cent with 5,810,000 red cells, 6,200 white cells and normal differential count.

Chest x-ray inspection revealed only slight change in the original lesion seen in 1945 (Fig. 2). He refused medical advice and was not heard from again until June, 1949, when he saw a physician, complaining of the same anterior left chest pain. He stated that he had had pneumonia six months before (January, 1949), which lasted two weeks and after this he felt better and went back to work. He retained slight cough productive of a small amount of thick yellowish sputum. He noticed that he became progressively more easily fatigued and that he had lost 26 pounds in weight in six months. He finally became so weak that he could not do his work. He did not take his temperature during this period, but felt that it was somewhat elevated at times, especially in the evenings.

In the interim from January to June 1949, the sputum was repeatedly blood-streaked and occasionally bright red and foamy. He was bronchoscoped at this time and no abnormality observed. A Papanicoloau smear for cancer cells was negative as well as serology, histoplasmin and coccidoidin tests. He had a three plus reaction to 0.1 milligrams of tuberculin.

On admission to the hospital (July 10, 1949), physical examination revealed a poorly nourished white male, 39 years of age; Blood pressure was 130/90; there was marked dulness in the left apex with rales heard both anteriorly and posteriorly in the left side throughout the lung field. The remainder of the physical examination was noncontributory. Laboratory work revealed 11.1 Grams or 66 per cent hemoglobin; red blood count of 4,000,000; white blood count of 12,400; with lymphocytes, 32; monocytes, 3; polymorphonucular leucocytes, 65; urinanlysis showed a

few epithelial cells; six to eight pus cells; urobilinogen was present in increased amounts. X-ray inspection of the chest (Fig. 3) revealed a suggestion of a neoplastic lesion in approximately the same area of the lung in which the possible tuberculous process was discovered.

It was decided that after preparing the patient with several blood transfusions, an exploratory thoracotomy should be done with intention of removing the left lung if it proved to be an operable lesion. Exploration was accomplished through the sixth rib. Despite the rather large size of the lesion, total left pneumonectomy was performed, removing the hilar lymph nodes. Frozen sections showed them to be negative for carcinoma. It was necessary to remove a considerable portion of the parietal pleura over the apex of the lung, together with the lung, because they were so closely adherent. Individual dissection and ligation of vessels was done. The bronchus was closed with silk and covered with pleura. The patient was given 1500 cc. of blood on the table. He was discharged the 15th postoperative day in good condition. The pathologist's report of the surgical specimen (Fig. 4) described it as "immediately beneath the apex—a rounded, firm, well circumscribed mass, measuring 8.5 cm. in diameter, having a mottled, gray, yellow and red cut surface . . ." "one of the larger branches of the upper lobe bronchus contained soft, friable tumor tissue . . ." "immediately adjacent to the tumor there was a cavity measuring 2 cm. in greatest dimension which had an indurated wall. This contained yellow caseous material."

Microscopic examination (Fig. 5) showed the tumor to be a "rather poorly differentiated bronchogenic carcinoma of squamous cell type. The section from the wall of the cavity showed caseation necrosis, surrounded by some epithelioid cells and lymphocytic infiltration. Smears from the necrotic material were positive for acid-fast organisms."

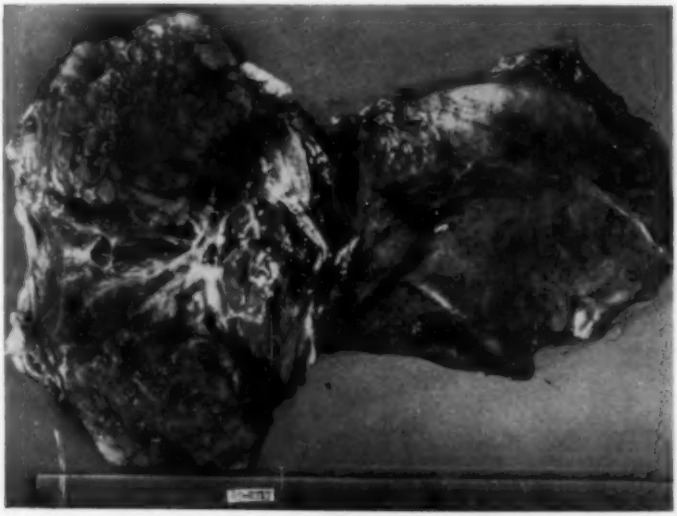


FIGURE 4

An empyema required drainage the fifth day postoperatively. This patient's prognosis ordinarily would have been viewed with some degree of optimism since the tumor mass was peripherally located in the lung and no hilar nodes were found to contain neoplastic infiltration; however, the fact that it was so closely adherent to the parietal pleura over the dome of the lung, and that it was a rather large sized growth forced us to take a dim view of this patient's chance for survival.

This guarded prognosis has since been substantiated on a routine postoperative checkup (September, 1949) by the appearance of metastic nodes in the supraclavicular region.

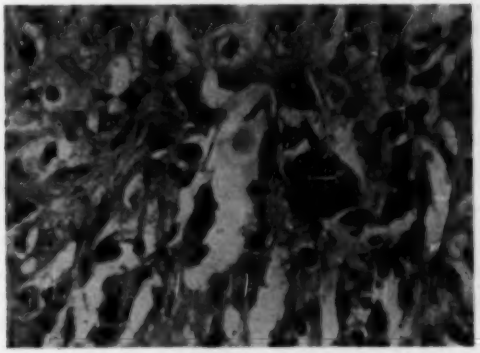


FIGURE 5

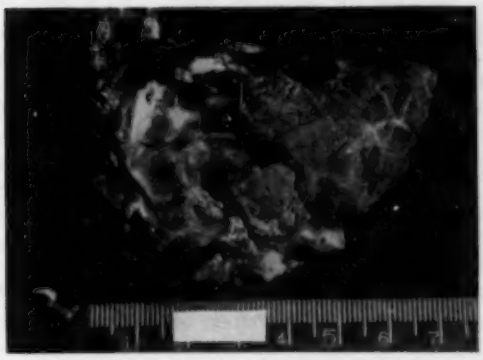


FIGURE 6

General Discussion

In this case, we were presented with an individual developing symptoms of pulmonary tuberculosis at the age of 35 years. While the diagnosis of pulmonary tuberculosis was never absolutely established by positive sputum during the entire four years of his

illness, his lung findings on x-ray and physical examination and his clinical course were fairly suggestive of acid-fast infection. The finding at operation of acid-fast bacilli in a typical cavity proved this to be a correct assumption.

The fact that the disease course did continue over four years time bespeaks some priority for the tuberculosis, although both the tuberculosis and the carcinoma could conceivably have coexisted for the entire time. We feel, however, it is most probable that the cancer began within the last six to 12 months of his illness, if the final size of the tumor, and the lack of spread elsewhere, correlated with the clinical course, can be considered as criteria.

In 1949, chest pain, blood-streaked sputum, great weight loss, anemia and marked fatigue, out of proportion to his lesion, together with an x-ray shadow suggesting neoplasm, forced us to consider bronchogenic carcinoma as our working diagnosis.

The fact that the patient was relatively young for bronchogenic carcinoma (in Fried's series, 13 cases; in Robbins and Silverman's series, 12 cases of coexisting pulmonary carcinoma and tuberculosis not one was younger than 45 years); that the tumor was peripherally located; that a negative bronchoscopic examination and a Papanicolaou smear were obtained plus a rather typical history of tuberculosis—were all "herrings across the trail" in the diagnosis of the bronchogenic carcinoma. As Fried has suggested, bronchogenic carcinoma should be suspected to coexist with pulmonary tuberculosis, or exist by itself simulating tuberculosis, when the patient past middle age develops chest pain and blood-streaked sputum, profound anemia, fatigue, weight loss, all out of proportion to the tuberculous lesion. Signs of further advanced cancer such as nodules of carcinoma in the clavicular region, presence of Horner's syndrome or distant metastes, paralysis of diaphragm and vocal cords, involvement of trachea, etc., easily make the malignant process apparent and also demonstrate an inoperable situation. Some surgeons (DeBakey, Ochsner and Dixon), however, feel that paralysis of the diaphragm and vocal cords does not always indicate an inoperable case. Jaffe cites one of his cases in which the first symptom was a right lower quadrant pain simulating appendicitis. It proved to be a metastasis to the iliac bone from a small bronchogenic carcinoma superimposed on bilateral tuberculosis. Early diagnosis is paramount if the patient is to have a chance for survival. X-ray inspection of the chest, especially comparative studies, are of great value in the diagnosis of pulmonary diseases.

Watson, Papanicolaou, et al, state that sputum and bronchoscopic washings for tumor cell presence will provide the correct diagnosis in about 60 per cent of all cases of bronchogenic car-

cinoma and bronchoscopic biopsies (whenever a lesion is visualized) —86 per cent correct diagnosis. Other examiners (Woolner and Clerf) claim up to 90 per cent. Early pneumonectomy with removal of the hilar and mediastinal nodes is the only hopeful treatment of bronchogenic carcinoma.

The advances in recent years in thoracic surgery, anesthesiology and our knowledge of pulmonary physiology have made pneumonectomy a relatively safe operative procedure.

SUMMARY

1) Bronchogenic carcinoma may be easily masked by pulmonary tuberculosis.

2) The incidence of coexisting bronchogenic carcinoma and pulmonary tuberculosis likely occurs more often than is generally believed.

3) The association of the two diseases is probably coincidental.

4) A case report is given of pulmonary disease existing for a period of four years in which pneumonectomy was finally performed. Two diseases were found to exist in the same lung. The tuberculosis was thought to have preceeded the cancer by a considerable period of time.

5) The problems encountered and methods used in the diagnosis are discussed.

6) Very early diagnosis and total pneumonectomy offer the only chance for survival.

RESUMEN

1) El carcinoma bronquiogénico puede enmascararse facilmente como tuberculosis.

2) La incidencia de carcinoma bronquiogénico y tuberculosis coexistentes es mayor de lo que generalmente se cree.

3) La asociación de las dos enfermedades probablemente es una coincidencia.

4) Se presenta un caso en el que la tuberculosis existía por un periodo de cuatro años en el que se hizo al fín la neumonectomía.

5) Se discuten los problemas y los métodos usados en el diagnóstico.

6) El diagnóstico muy temprano y la neumonectomía total ofrecen la única posibilidad de sobrevida.

RESUME

1) Un carcinome bronchique peut être facilement masqué par une tuberculose pulmonaire.

2) Le fait de la coexistence du carcinome bronchique et de la tuberculose pulmonaire arrive plus souvent qu'on ne le croit généralement.

3) L'association des deux maladies est sans doute une coincidence.

4) L'auteur rapporte un cas de tuberculose existant depuis 4 années, et pour laquelle on fit une pneumonectomie. On trouva le poumon atteint des deux maladies. On pense que la tuberculose avait précédé le cancer depuis longtemps.

5) L'auteur discute les problèmes et les méthodes diagnostiques.

6) Un diagnostic précoce et une pneumonectomie totale offrent seuls une chance de survie.

REFERENCES

1 Carlson, H. A. and Bell, E. T.: "Statistical Study of the Occurrence of Cancer and Tuberculosis in 11,195 Post-mortem Examinations," *J. Cancer Research*, 13:126, 1929.
2 Clerf, L. H.: "Progress in Bronchology," *J.A.M.A.*, 136:733, 1948.
3 Cooper, F. G.: "The Association of Tuberculosis and Carcinoma," *Am. Rev. Tuberc.*, 25:108, 1932.
4 Feld, D. D. and O'Malley, V.: "Bronchogenic Carcinoma," *Dis. Chest*, 15:450, 1949.
5 Fried, B. M.: "Bronchogenic Cancer Combined with Tuberculosis of the Lungs," *Am. J. Cancer*, 23:247, 1935.
6 Fulton, D. and Rolleston, C.: "Bronchial Carcinoma in a Case of Pulmonary Tuberculosis Undergoing Artificial Pneumothorax Treatment," *Brit. J. Tuberc.*, 40:129, 1946.
7 Graham, E. A.: "Pulmonary Tuberculosis Combined with Carcinoma of the Lung," *J. Missouri M. A*, 26:70, 1929.
8 Jaffe, R. H.: Pathological Conference held at the Cook County Hospital. Edited by Chester C. Guy, M.D. Cook County Hospital Intern's Alumni Association. *Mum's Print Shop, Inc.*, Evanston, Illinois, 1940.
9 Moak, H.: "On the Occurrence of Carcinoma and Tuberculosis in the Same Organ or Tissue," *J. M. Research*, 8:128, 1902.
10 Ortel, H.: "On the Relative Local Influence of Coexisting Tuberculosis Inflamation and Cancer in the Lung," *J. M. Research*, 25:503, 1911-12.
11 Ochsner, A., DeBakey, M. and Dixon, D. L.: "Primary Cancer of the Lung," *J.A.M.A.*, 135:321, 1947.
12 Pearl, R.: "Cancer and Tuberculosis," *Am. J. Hyg.*, 9:97, 1929.
13 Ritterhoff, R. J.: "Malignant Neoplasm Simulating Pulmonary Tuberculosis," *Cincinnati J. Med.*, 24:197, 1943.
14 Robbins, E. and Silverman, G.: "Coexistent Bronchogenic Carcinoma and Active Pulmonary Tuberculosis," *Cancer*, 2:65, 1949.
15 Ross, H. (Quoted from Fulton, D. and Rolleston, C.).
16 Tudor-Edwards, A. (Quoted from Fulton, D. and Rolleston, C.).
17 Valle, A. R. and White: "Pulmonary Tuberculosis Simulating Bronchogenic Carcinoma: Report of Four Cases," *Am. Rev. Tuberc.*, 55: 449, 1947.
18 Watson, W. L., Cromwell, H., Craver, L. and Papanicolaou, G. N.: "Cytology and Bronchial Secretions—Its Role in Diagnosis of Cancer," *J. Thoracic Surg.*, 18:113, 1949.
19 Woolner, L. B. and McDonald, J. R.: "Bronchogenic Carcinoma Diagnosis by Microscopic Examination of Sputum and Bronchial Secretions: Preliminary Report," *Proc. Staff Meet., Mayo Clinic.*, 22:369, 1947.

Mediastinal Teratoma

FRANK T. FRALICK, M.D., F.C.C.P.*
Rome, Georgia

HUGH S. WELSMAN, M.D.**
Toronto, Canada

As mass chest x-ray surveys gain in popularity their value other than in detecting cases of pulmonary tuberculosis, which has been considered their primary purpose, is gradually being recognized. It is becoming generally known that this is one of the most productive means through which early diagnosis of tumor in the chest is made. In some surveys tumor of the mediastinum has been seen as frequently as active pulmonary tuberculosis. An important group of these, the teratoma, is illustrated by the following cases which were discovered when totally unsuspected.

Case 1: S.S. (Fig. 1). This 38 year old housewife had a photofluorogram of her chest in a community mass survey on September 27, 1948. Because of the abnormality in her chest she received further clinical examination and was then referred to a general hospital for the treatment of a suspected dermoid cyst. She was admitted to the Toronto Western Hospital on November 16, 1948. She stated that she was well except for slight increase in susceptibility to fatigue during the past year. She also possibly noticed shortness of breath slightly more than normal on climbing stairs but this was indefinite. She had about one cold a year lasting approximately two weeks with some cough but no sputum. Examination of the chest revealed an area of dullness between the second and fifth ribs anteriorly on the left side extending laterally from the sternum to the midclavicular line. No breath sounds could be heard over this area. A systolic murmur was detected over the base of the heart extending to the great vessels on the left side.

On November 16, 1948 thoracotomy was performed. A tumor about the size of a large orange was found in the anterior mediastinum bound down by many adhesions especially posteriorly. It was removed.

Pathological examination revealed a specimen consisting of a large firm cystic mass 9 cm. in diameter by 6.5 cm. in thickness. Its surface was of a mottled yellowish-gray color. On section the wall was found to be very hard and gritty. The contents were thick, yellowish-gray in color, curdy and greasy in nature. The sebaceous material contained gray hair. The cyst wall was from a fraction of a mm. to 1.3 cm. in thickness. Microscopic inspection showed the cyst wall to be composed of dense fibrous tissue containing deposits of calcium and showing hyaline degeneration. In some areas were collections of cholesterol. One area showed bone formation. Collections of lymphoid tissue were present. The specimen was considered to be a dermoid cyst.

---

*Battey State Hospital, Rome, Georgia, formerly with Gage Institute, Toronto, Canada.
**Gage Institute, Toronto, Canada.

The patient made an uneventful recovery and was discharged 16 days following operation.

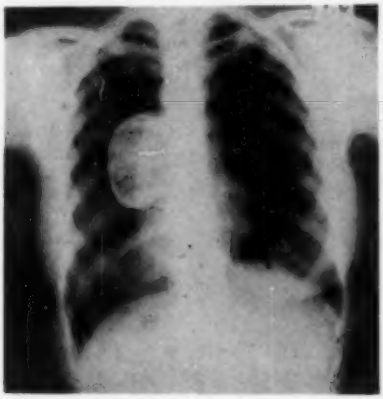


FIGURE 1, CASE 1: Showing calcified wall and irregular densities in mediastinal tumor.

Case 2: R.P. (Fig. 2). This 16 year old boy had a photofluorogram of his chest in a survey of High School students on February 15, 1946. He was examined clinically on March 1, 1946. He had no symptoms and no abnormality was detected on physical examination. The abnormal shadow seen in the x-ray film was thought to be due possibly to an abnormality of the aorta on the right side and he was referred to a general hospital for further investigation. He however failed to follow this advice. He was not seen again until December 4, 1947 when he reported in another mass survey. Following the second photofluorogram of his chest he was again examined clinically on January 8, 1948. He stated that on several occasions during the past year he had noticed mild attacks of pain on the right side of the chest with chills. The mass was now considered to be a possible dermoid cyst and the patient was again referred to a general hospital. He again failed to cooperate. However on January 18, 1948 he developed severe pain on the right side of the chest, chills and nausea, and he was admitted on January 19, 1948 to the Toronto General Hospital.

On admission he appeared moderately though not accutely ill. His rectal temperature was 103 degrees F. Movement of the right side of the chest was slightly decreased and there was dullness to percussion just to the right of the sternum at the level of the third rib and fourth anterior interspace. His WBC was 10,300. Fluoroscopy revealed a non-pulsatile rounded mass in the anterior portion of the chest on the right side close to the mediastinum. At this time it was thought that he had a dermoid cyst of the anterior mediastinum with associated pneumonitis and pleuritis or possibly an infected dermoid with pleuritis and pericarditis. Penicillin was administered intramuscularly for two weeks at which time his temperature had returned almost to normal and his symptoms had decreased. Further examination of the primary lesion now included x-ray inspection. This demonstrated a mass anteriorly in the right mid-lung field displacing the minor fissure downward and the heart to the left.

FIGURE 2a FIGURE 2b FIGURE 2c

Figure 2, Case 2: (a) March 1, 1946: Showing enlargement of right side of mediastinum thought possibly due to abnormalty of aorta.—(b) January 8, 1948: Showing increase in size of mediastinal tumor.—(c) Lateral view showing tumor in anterior mediastinum.

The mass measured about 10 cm. in diameter and there were minor associated pleural changes. Lipiodol bronchogram indicated that the mass was extrapleural. A needle was inserted into it and 70 cc. of cloudy, brownish fluid, containing many red blood cells but no malignant cells, were obtained. Pneumothorax was then induced on the right side. This revealed the mass to be extrapleural and attached to the anterior chest wall or parietal pleura.

On March 2, 1948 thoracotomy was performed on the right side. A large inoperable malignant tumor was found extending upward about the great vessels and into the right pleural cavity to compress the right lung. Biopsies were taken and were reported as follows: "In the material received are innumerable large and smaller sheet-like aggregations of

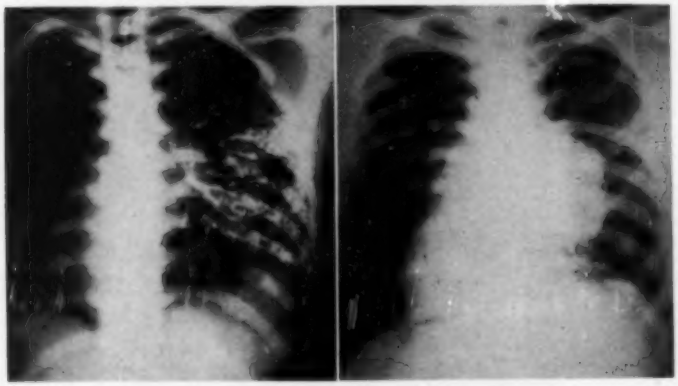


FIGURE 2d FIGURE 2e

Figure 2d, Case 2: February 4, 1948: Lipiodol bronchogram showing tumor to be extrapleural.—(e) March 15, 1948: Two weeks following operation.

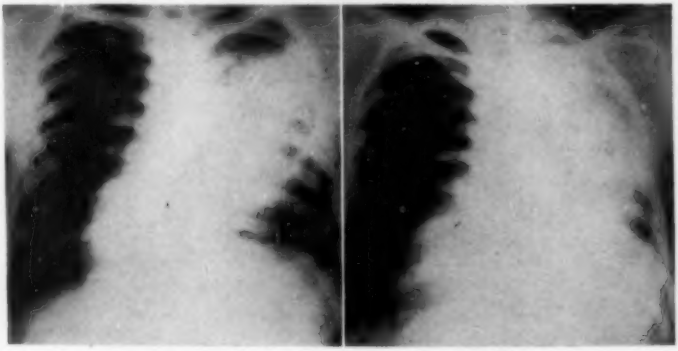


FIGURE 2f FIGURE 2g

Figure 2f, Case 2: June 18, 1948: Three months following operation. (g) October 8, 1948: Two months before death.

atypical epithelial cells with abundant vacuolated rather basophilic cytoplasm and large vesicular pleomorphic and polymorphic nuclei. Mitotic figures occur with relative frequency. The tumor cells are unassociated with any epithelial pearls or ectopic depositions of keratin material. There has occurred however a very dense sclerotic collagenous reaction about the islands of tumor cells which has completely obliterated any pulmonary architecture. It is therefore impossible to determine whether this lesion actually arises from the lung. It may of course be a malignant teratomatous lesion from the mediastinum. There can be no question of its malignant nature."

The patient made a good recovery from the operative procedure. Previous to his discharge from the hospital on March 18, 1948 high voltage radiotherapy was commenced. This was continued in the Out-Patient Department. He however developed extreme weakness, loss in weight, nausea, and cough productive of yellow sputum. On December 6, 1948 he died at home. Permission for necropsy could not be obtained.

As the division between dermoid cyst and teratoma is not a rigid one, many borderline cases being recognized, it is convenient to describe all of these tumors as teratoma and to qualify the term according to the type.

The first example of a tumor of this kind to be recorded—a dermoid cyst of the mediastinum—was described by J. A. Gordon in 1823. It occurred in a 21 year old woman and contained sebaceous matter, hair, bone and teeth. Since then for a century and a quarter this group of tumors has provided a fascinating subject for study. By 1869 they had become clearly recognized as a clinical entity—a case having been correctly diagnosed during life by the expectoration of hair. Although previously considered to occur relatively uncommon in the mediastinum they are now being encountered more frequently through increased use of the x-ray and effectiveness of chest surgery. Only 251 cases have been reported in the literature.

Etiology

The genesis of teratoma has been a fertile field for speculation and the various hypotheses regarding their origin indicate our lack of knowledge in this regard. Their development, as Nicholson states, is not comparable to that of the embryo nor do they in general contain any of the regions characteristic of the body. They are not the result of the orderly changes which result in the normal soma. They are, he believes, "pathological manifestations of physiological growth."

As will be remembered normal development of the amphibian egg (from which hypothetical diagrams of development in man can be drawn) proceeds by division of the fertilized egg to the formation of the solid morula. The inner cells of this become vacuolated to form the hollow blastula which invaginates to form

the gastrula. The gastrula is the beginning of the three presumptive germ layers when distinctive types of cells first become recognizable differing both structurally and functionally. Ewing warns us that the germ layers need not necessarily remain rigidly specific—that the separation of the three layers may be incomplete and that portions of one layer may be carried over into the other. Spemann has concluded from his experiments that although the direction which the development of the tissues of each of the three germ layers takes is predetermined possibly as far back as the blastula or even the fertilized egg—the surrounding medium has a specific influence. He has described this as the inducing power of adjacent tissues this inducing action being transferred by a chemical substance. He believes that when tissue becomes dislocated it is not only subject to the action of the inducing powers of its new surroundings but its capacity to react to them may be altered. As a result it may differentiate into structures that are wholly foreign to that region. Under abnormal conditions organoid structures but never complete organs may be induced. In some such manner the wierd mixture of cells in a teratoma may be explained. Ewing believes that extragenital teratoma may be derived from "isolated nearly totipotent blastomeres or from early budding of the blastoderm or multipotent material of distinct regional stamp." However the problem remains far from being solved as Rusby is careful to emphasize.

Teratoma of the mediastinum has been considered by some to originate within the third and fourth branchial clefts. It almost always occupies the region of the thymus gland and has frequently been found in intimate relationship with it. As the thymus is the only branchiogenic structure to descend into the anterior mediastinum it has been concluded by some that mediastinal teratoma has its origin in connection with faulty embryogenesis of this organ. On the other hand location of the primary tumor on or in position of the lung rather than chiefly within the mediastinum occurs in cases reported by Harrington and others. While all the elements of the mediastinal teratoma may be of thymic origin this need not necessarily be the case. The role of the thymus may be purely mechanical serving only to bear the primordia of the tissue from the cervical region down into the thorax with the heart and lungs.

Pathology

"Teratomata are the most complex and monstrous of tumors. They introduce us into a world of phenomena undreamed of in normal evolution. They lead to an understanding and just appreciation of the countless unending potentialities of living matter."

So wrote Nicholson in 1934. The term teratoma is commonly used to describe tumors including derivations of all three germ layers. There is, however, a large group of tumors of presumably the same etiology but which include demonstrable multiple elements derived from but two or even a single germ layer. In many of these instances the failure to demonstrate additional elements is attributable to: (1) Extensive necrosis of the tissues the actual nature of which it is obviously impossible to determine. (2) Early overgrowth of a single germ layer. "Since the bulk of the early embryo is composed of ectoderm the overgrowth of this germ layer in the development of a teratoma is a natural result" (Ewing). (3) Failure to take sufficient section for microscopic study.

Teratoma may exhibit any combination of tissues intermingled without apparent reason. They are predominantly cystic and the uni- or multilocular cysts may be lined with stratified squamous, cuboidal or columnar epithelium. Sebaceous material and hair are usually found in the cysts. In the solid portion bone, cartilage, teeth, muscle (both smooth and striated), nervous tissue, and occasionally rudimentary organs, are found. The tissue may be of adult or embryonal type. Both the so-called cystic and solid (or immature "embryonic") teratomata are potentially malignant. According to Rusby 70 per cent of malignancies arise in the solid type, 30 per cent in the cystic type. Fox and Hospers found in a collection of two hundred teratomata 55 per cent were single dermoids, 25 per cent complex benign dermoids, and 20 per cent malignant tumors. The great majority of primary malignant teratomata occur in males in the proportion of 8 to 1 and in the age group 18 to 25 years. Although originating in embryonic life a teratoma may remain small and dormant throughout life, being found quite unexpectedly at autopsy. On the other hand it vies with lipoma for being the largest of mediastinal tumors—the adaptability of the heart and lungs to its encroachment being a striking attribute. The tendency to grow occurs in adolescence and early adult life. A satisfactory explanation of the remarkable growth of mediastinal teratoma in the young adult has not been found although various hormonal factors have been called into account. Malignant change is thought to be contemporary with rapid increase in size of the benign teratoma. Malignancy may represent the degeneration of a single element of the tumor most often epithelial but it usually dominates the picture. Differences with respect to the degree of differentiation and rapidity of growth of various parts of the teratoma may occur. Thus true extragenital chorionepithelioma found usually in males and which according to Ewing is merely the embryonal equivalent of adult ectoderm probably always arises in teratomatous tissue. Probably purely

mesodermal or ectodermal tumors which are really of teratomatous derivation occurring in the mediastinum have passed as of unexplained origin. Among these may be included some of the fibromata, cystic lymphangiomata, complex sarcomata, and undifferentiated blastomata which have been described in the literature. (According to Ewing all chondromata in the testes are teratomatous). Metastases may be complex or composed of one or two elements only.

Onset of infection in a teratoma is usually associated with rupture into a bronchus or the pleural cavity and is liable to follow the formation of a fistula. Accumulation of fluid within the teratoma may follow infection without the formation of a fistula and may in some cases explain the sudden increase in size of these tumors. Infection may be spread from the lung by the bloodstream.

Symptoms and Signs

Although teratoma of the mediastinum is believed to result from faulty development occurring in embryonic life it is well recognized that the majority lie dormant within the chest for many years and only become obtrusive when adolescence or early adult life is reached. Malignant change, or inflammation in its neighbourhood resulting in fluid secretion within the tumor, results in its increase in size and consequent inconvenience. Progressive enlargement will ultimately produce symptoms due to pressure of the mass upon neighbouring structures within the thorax. The initial symptoms of both benign and malignant teratoma are similar—paroxysmal cough, dyspnoea on exertion, or as suffocative attacks or periodic asthma, sensation of pressure in the chest or pleuritic or anginal type of pain and haemoptysis being the most common. Symptoms are usually intermittent and gradually progressive. There may be enlargement of the veins of the neck, shift of the trachea and heart, dullness on percussion and suppression of breath sounds. Expectoration of hair is the only pathognomonic sign of this tumor. Sebaceous material, or fat droplets may be present in the sputum. Pleural effusion, empyema, lung abscess or bronchiectasis may mask teratoma which is the underlying cause. The onset of infection may be dramatic and grave in outcome resulting in hectic fever, profuse offensive sputum, haemoptysis and eventual death. A positive Aschheim-Zondek test and gynecomastia have been recorded with teratomatous chorionepithelioma in male patients. Froelich's syndrome may be present.

Radiology is contributing in ever increasing measure to the early and accurate recognition of intrathoracic tumors. There is every likelihood of an increase in the number of symptomless tumors being recognized with the use of mass radiography. Teratoma

occupies the anterior compartment of the mediastinum beneath the sternum. There are few intrathoracic tumors similarly disposed. It is usually globular or circular in shape with clear-cut edges. The main mass of the tumor as a rule has a homogeneous density but occasionally this uniformity is interrupted by small more opaque areas which may represent teeth or plaques of bone. Areas of calcification in the wall are also opaque to x-ray and rarely the wall is wholly composed of calcareous material resembling a shell. Fluid level may indicate communication with a bronchus. An irregular lobulated appearance may be indicative of a malignant teratoma.

Differential Diagnosis

It may be necessary to differentiate teratoma from substernal thyroid gland and in this basal metabolism may be helpful. Thymoma has usually a comparatively short history associated with signs and symptoms of malignancy and is locally invasive. Both this and lymphosarcoma are radiosensitive, the teratoma remaining unaffected by x-ray. Saccular aneurysm of the first part of the aorta extending forward may simulate teratoma and may be distinguished by auscultatory findings, fluoroscopy, age and blood Kahn. Lipoma may be distinguished by aspiration biopsy, cholesterol crystals, as well as epidermal elements, etc., being found in a teratoma. Chondroma of the sternum or costal cartilage is rare but may be confusing. Hydatid cyst may be differentiated by the expectoration of sputum containing hooklets or suspected by the combined use of the complement fixation and Casoni intracutaneous tests. An inflammatory pericardial cyst resulting from previous pericarditis, more often seen on the right side of the heart, often pulsates. Encysted interlobar empyema, tuberculous abscess from spinal caries, solitary cyst of the lung or bronchus, pericardial celomic ("spring water") cyst, oesophageal or gastroenteric cyst, achalasia of the cardia of the stomach with megaoesophagus may be misinterpreted as representing teratoma of the mediastinum.

Treatment

The only form of treatment that will prove of any lasting avail for teratoma of the mediastinum is surgical intervention. All these tumors are potentially malignant and such change may occur even after a long period. Usually they should be removed whether or not they are producing symptoms. Even if they remain benign their course is often progressive and they may ultimately produce serious complications or chronic invalidism or inflammatory change resulting in fatal haemorrhage or cachexia and death.

No case can be found in the literature in which radical surgery has resulted in permanent cure after malignant change has taken place.

SUMMARY

1) Two cases of mediastinal teratoma are presented—one cystic and benign, the other solid (or immature) showing carcinomatous change.

2) The etiology of teratoma is unknown but may be related to the inducing power of surrounding tissue on displaced cells during embryogenesis.

3) Chest x-ray inspection such as that provided by mass surveys is the most productive means of early diagnosis of this condition.

4) Symptoms appear with increase in size of the tumor such as occurs in the presence of infection or malignant change.

5) Teratoma may be masked by secondary infective processes of which it is the underlying cause in the chest.

6) The tendency to increase in size in adolescence and early adult life is frequently due to malignant change. In one large series 20 per cent showed this change. It is more common in males in the proportion of 8 to 1.

7) Surgical treatment should be instituted early. After malignant change has occurred there has been no case reported in which radical surgery has resulted in permanent cure.

We wish to express our appreciation to Dr. F. G. Kergin, Associate Professor of Surgery, University of Toronto, who made available the case records of the Toronto General Hospital in Case 2, also to Dr. R. C. Laird, Associate Professor of Surgery, University of Toronto, who provided information from the records of the Toronto Western Hospital in Case 1, also to Dr. A. C. Singleton, Professor of Radiology, University of Toronto, for the use of some of his chest x-ray films for reproduction with some of our own in Case 2.

RESUMEN

1) Se presentan dos casos de teratoma mediastinal, uno cístico y benigno, el otro sólido (no maduro) que muestra cambio a carcinoma.

2) La etiología del teratoma es desconocida pero puede estar en relación al poder de inclusión del tejido circundante sobre celdillas desplazadas durante la embriogénesis.

3) El examen a los rayos X como el que se hace en los catastros radiográficos es el mejor medio para diagnósticar estas condiciones de manera temprana.

4) Los síntomas aparecen al aumentar el volumen del tumor como ocurre cuando hay infección o transformación maligna.

5) El teratoma puede ser enmascarado por un proceso infeccioso del cual puede ser el trastorno subyacente.

6) La tendencia a aumentar de tamaño en la adolescencia y al principio de la vida adulta es frecuentemente debida a aparición de malignidad.

En una serie larga el 20 por cento mostró este cambio. Es más común en los varones en la proporción de 8 a 1.

7) El tratamiento quirúrgico debe instituirse de inmediato. Después de la transformación a maligno no ha habido informe de que la cirugía radical produzca una cura permanente.

RESUME

1) L'auteur présente deux cas de tératomes médiastinaux l'un kystique et bénin, l'autre solide (ou immature) montrant une modification carcinomateuse.

2) L'étiologie du tératome est inconnue, mais peut être reliée au pouvoir d'induction des tissus adjacents sur les cellules déplacées pendant l'embryogénèse.

3) Pour établir un diagnostic précoce, la radiographie pulmonaire prise au cours d'examens systématiques est le moyen le plus efficace.

4) Les symptômes apparaissent lors de l'accroissement de la taille de la tumeur, comme il arrive en présence d'une infection ou d'une évolution maligne.

5) Le tératome peut être caché par des processus infectieux secondaires du thorax, dont il est en fait la cause.

6) La tendance à s'accroitre en volume chez l'adolescent ou le jeune adulte est souvent due à une évolution maligne. Cette évolution s'est produite dans 20% des cas d'un matériel important d'observations. Elle est plus fréquente chez les hommes dans la proportion de 8 pour 1.

7) Le traitement chirurgical devrait être institué précocement. Après que l'évolution maligne se soit produite, il n'y a aucun cas de guérison post-opératoire.

REFERENCES

1 Willis, R. A.: "The Structure of Teratomata," *Jour. Path. and Bact.*, 40:1, 1935.
2 Nicholson, G. W.: "The Histogeny of Teratomata," *Jour. Path. and Bact.*, 32:365, 1929.
3 Nicholson, G. W.: "Studies in Tumor Formation," *Guy's Hospital Reports*, 84:389, 1934.
4 Nicholson, G. W.: "Studies in Tumor Formation," *Guy's Hospital Reports*, 84:140, 1934.
5 Spemann, H.: "Embryonic Development and Induction," *Yale University Press*, New Haven, Connecticut, 1938.
6 Doran, W. T. and Lester, C. W.: "Mediastinal Teratomata," *Jour. Thor. Surg.*, 8:309, 1938-39.
7 Dann, D. S., Lockwood, I. H., Neibling, H. A. and Walker, J. W.: "A Teratoid Tumor of the Chest," *Radiology*, 44:585, 1945.

8 Schlumberger, H. G.: "Teratoma of the Anterior Mediastinum," *Arch. of Path.*, 41:398, 1946.
9 Rusby, N. L.: "Dermoid Cysts and Teratomata of the Mediastinum," *Jour. Thor. Surg.*, 13:169, 1944.
10 Fox, J. P. and Hospers, C. A.: "Solid Teratoid Tumors of the Anterior Mediastinum," *Am. Jour. of Cancer*, 28:273, 1936.
11 Houghton, J. D.: "Malignant Teratomata of the Mediastinum," *Am. Jour. of Path.*, 12:349, 1936.
12 Harrington, S. W.: "Surgical Treatment in Eleven Cases of Mediastinal and Intrathoracic Teratomas," *Jour. Thor. Surg.*, 3:50, 1933.
13 Wheeler, D.: "Dermoid Cyst of the Mediastinum with Rupture into the Pleural Cavity," *Canadian Med. Assn. Jour.*, 41:235, 1939.
14 Gordon, J. A.: "A Case of Tumor in the Anterior Mediastinum Containing Bone and Teeth," *Royal Medical and Chirurgical Society of London Transactions*, 13:12, 1823-27.
15 Barret, M. R. and Thomas, D.: "Pulmonary Hydatid Disease," *British Jour. of Tuberc. and Dis. of Chest*, 38-39:39, 1944-45.
16 Bradford, M. L., Mahon, H. W. and Grow, J. B.: "Mediastinal Cysts and Tumors," *Surg., Gynec. and Obst.*, 85:467, 1947.
17 Ewing, J.: "Neoplastic Diseases," *W. B. Saunders Co.*, 1041, 1940.
18 Ewing, J.: "The Thymus and Its Tumors," *Surg., Gynec. and Obst.*, 22:461, 1916.
19 Bailey, F. R. and Miller, A. M.: "Textbook of Embryology," *Wm. Wood and Co.*, 35, 1929.

Cysts of the Pleura

WALLIS L. CRADDOCK, M.D.*
Fort Logan, Colorado

In contrast to the now frequently appearing and diagnosed pulmonary and bronchial carcinomata, primary tumors of the pleura are rare. Clinical differentiation of malignant tumors of the pleura from malignant tumors of the lung is essential. The most common malignant tumors of the pleura are the endotheliomata, the course of which resembles the course of an exudative tuberculous pleurisy.

Benign tumors of the pleura (fibromata, osteomata, chondromata) seldom produce clinical manifestations and, therefore, are of little clinical importance. In unilateral opacities seen in the chest film, it is often difficult to make a diagnosis of specific pleural tumors. In the differential diagnosis of primary benign and malignant tumors of pleura must be included metastatic tumors, tumor-like tuberculosis, tumors of the chest wall, pleural effusion, echinococcus cysts of the pleura and the group of congenital cysts. It is the purpose of this paper to describe an addition to the group of benign tumors of the pleura, the simple cyst, which has caused some debate in recent years regarding its true nature.

Fehr,[1] in 1936, described a case in which roentgen inspection of the thorax disclosed a thin, sharply circumscribed shadow in the left lower pulmonary field. This lesion was situated directly above the diaphragm at the ventral side of the thorax. The patient also had a rectal carcinoma. A preliminary diagnosis of "solitary pulmonary metastasis" was abandoned, and it was assumed that some benign tumor, independent of the rectal carcinoma, was present. The patient died from surgery for the carcinoma. Autopsy disclosed a serosal cyst emanating from the diaphragmatic pleura. It was considered to be a "malformation, probably of congenital origin." Freedman and Simon,[2] in the same year, also reported a case of a single large cyst occurring in the lower zone of the left lung field. Similar cases were later reported by Pickhardt[3] and Addey.[4] In none of these cases was there evidence of connection of the cyst to pericardium.

---

*From the Medical Service, Veterans Administration Hospital, Fort Logan, Colorado, and the University of Colorado Medical Center, Denver, Colorado. Sponsored by the Veterans Administration and published with approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Reported cases of cysts of the pericardium and mediastinum closely resembling those described by the above authors now total 18.[5-12,14-17,19-25] However, the modes of genesis in the cysts arising from pleura and pericardium are essentially the same. Eliaschewitch[6] was first to attempt an explanation of the genesis of these cysts:

1) The cysts may be derivatives of embryonal ducts. In the peritoneal cavity such formations are called enterocystomas.

2) These cysts may be considered as diverticuli of the serous cavities. For example, pressure by a hypertrophic heart may be responsible for such formations.

3) Lobular shapes of the cysts described in these earlier cases suggest a cystic transformation of a lipoma, although the cysts had walls lined with endothelium. A combination of a lipoma and lymphangioma could be responsible for such a formation.

4) Small cysts may be formed by a dilatation of glandular fissures developing in the wall of the serous cavity in the course of organization of a fibrinous exudate.

5) Inflammatory, papillary protrusions may undergo cystic transformation; these often follow pericarditis or pleuritis. Such an occurrence would explain the presence of fibrinous masses in the external layers, often noted.

6) The cysts are not real tumors but developmental malformations. The presence of other signs of excessive anlage in the form of a papilloma of the larynx supports this theory.

Terms given to these cysts include "simple cysts," "simple serous cysts" (after Curreri and Gale[15]), "spring water cyst" of Churchill,[12] "pericardiophrenic angle cyst" of Kinsella,[18] the commonly used term, "pericardial coelomic cyst" of Lambert,[14] and the earlier used term, "congenital diverticula." Haas[13] has set forth the theory that these "congenital diverticula" form at a point of weakness in the parietal pericardium where the fibrous layer passes out along the great vessels.

Lambert's explanation for pericardial cysts is based on a consideration of the embryology of the pericardium, as this structure arises from a series of disconnected lacunae which appear early in the embryo. These lacunae in the mesenchyme remain for a time as individual spaces, but eventually coalesce to form the pericardium coelom. If one of these lacunar cavities failed to merge, it could persist and give rise to a cyst in the vicinity of the pericardium, a "pericardial coelomic cyst." This view has remained unchallenged.

Case Report

N.M., male, age 42 years, entered the Veterans Administration Hospital, Fort Logan, Colorado, on January 7, 1948, after referral by the Veterans Administration Regional Office, Denver, because of routine photoroentgenogram finding of a small mass in the lower portion of the right lung field (Fig. 1). The veteran had reported to the Denver office for a pension examination for service-connected traumatic arthritis. He had a chest x-ray inspection one year previously and findings were negative. The patient was asymptomatic, and physical examination revealed no pathological findings. Laboratory examinations, including complete blood count, urinalysis, blood serology and erythrocyte sedimentation rate, were normal. Electrocardiogram, chest fluoroscopy, cardiac fluoroscopy, and upper gastro-intestinal series revealed nothing informative. Artificial pneumothorax and pneumoperitoneum were instituted and oblique x-ray view of the chest localized a small ill-defined shadow above the upper surface of the right leaf of the diaphragm, definitely not in the lung parenchyma.

An exploratory thoracotomy was performed on March 5, 1948, through the ninth intercostal space. A translucent cystic mass, measuring 2.0 x 1.0 x 1.0 centimeters, was removed intact by sharp and blunt dissection from the right diaphragmatic pleura. Following surgery, recovery was without complication.

Pathological Findings: The specimen appeared loculated, containing fluid and having a smooth wall. Microscopic sections showed a multilocular cystic structure composed of strands of elastic connective tissue fibers lined on the free surface by a single layer of endothelial cells. The structure was attached on one surface to bundles of striated muscle

FIGURE 1

fibers; there was no histological evidence of inflammation or malignancy.

Follow-up chest x-ray inspection at regular intervals, including a chest x-ray film taken March 21, 1950, have been negative. The patient has remained asymptomatic.

Discussion

Since thoracotomy has become an innocuous procedure, the true nature of circumscribed or "coin" lesions of the thoracic cavity can be determined after bronchoscopy, tomography and diagnostic pneumothorax and pneumoperitoneum have failed to give the diagnosis. The case described above illustrates this point.

It is obvious that cysts of the pleura and pericardium are accidentally found during the routine examination of the chest for some other suspected condition. These cystic lesions are of little consequence except in the differential diagnosis of space-occupying lesions of the thorax. Schein[24] asserts that, if the diagnosis can be positively made by thoracoscopy, operation is not indicated.

A brief differential diagnosis of cystic lesions which are found in the thorax would include:

1) Echinococcus cysts, which exhibit a characteristic lining membrane.
2) Embryonal cell-rest cysts from the respiratory and alimentary tracts, which show a cellular structure that readily identifies them.
3) Dermoid cysts and teratomas, which likewise have a distinctive composition.
4) Lymphangiomas, which represent a type of cystic growth resulting from malformation of a group of lymph vessels.
5) So-called "pericardial coelomic cysts," which arise from one of the primitive pericardial lacunae.

It would be well to review the types of congenital cysts found in the mediastinum. Laipply[17] has listed eight kinds: epidermoid, dermoid, teratoid, bronchial, esophageal, gastroenteric, "pericardial coelomic cysts" and cystic lymphangiomas. It is important that the last two be considered, since they are of mesodermal origin. These differ considerably in gross and microscopic structure:

"Pericardial coelomic cyst"

1) Simple in structure; usually unilocular.
2) Walls are thin layer of mesothelium, peeling readily from surrounding structures (well circumscribed).
3) Blood supply derived from pericardium.

Cystic lymphangioma

1) Complicated in structure; multilocular.

2) Walls of varying thicknesses; attempts at removal often associated with severe hemorrhages.

3) Blood supply derived from several sources.

SUMMARY

The differential points and diagnostic procedures to be evaluated in a case presenting a circumscribed or "coin" lesion of the chest have been given. The literature concerning the subject of cystic formations of the chest, including the so-called "pericardial coelomic cysts," has been reviewed. The literature has been extensively reviewed in the preparation of this paper. An interesting case of cyst of the pleura, operated, with follow-up, has been presented. This is the fifth such case which has been reported.

RESUMEN

Se presentan los elementos para el diagnóstico diferencial en un caso de lesión circunscrita en el tórax en forma de "moneda." Se revisa la literatura respecto de las formaciones quísticas del tórax, incluyendo los llamados "quistes celómicos pericárdicos." Se relata un caso de quiste de la pleura operado y observado después. Este es el quinto caso que se ha descrito.

RESUME

L'auteur donne les éléments d'un diagnostic différentiel dans un cas de lésion circonscrite ou lésion en forme de "pièce de monnaie" dans le thorax. Il donne un aperçu de la littérature qui traite le sujet de la formation des kystes dans le thorax, y compris les kystes dits "coelomiques péricardiques." Il présente un cas intéressant de kyste de la plèvre, opéré, et suivi de guérison. C'est le 5ème de cette nature qui ait été rapporté.

REFERENCES

1 Fehr, A.: "Pleural Cyst Simulating a Pulmonary Metastasis," *Deutsche Ztschr. f. Chir.*, 246:244, 1936.
2 Freedman, E. and Simon, M. A.: "Simple Cyst of the Pleura," *J. Roentgenol.*, 25:14, 1936.
3 Pickhardt, O. C.: "Pleuro-Diaphragmatic Cyst," *Ann. Surg.*, 99:814, 1937.
4 Addey, W.: "A Case of Pleural Cyst," *Brit. J. Radiol.*, 13:180, 1940.
5 Lenkeit, W.: "Cysts of Epicardium and Pericardium," *Centralbl. f. allg. Path. u. path. Anat.*, 44:97, 1928.
6 Eliaschewitsch, P. A.: "Case of a Cyst of Pericardium," *Virchows Arch. f. path. Anat.*, 270:868, 1929.
7 Dufour, H. and Mourrut, K.: "Cyst of the Pericardium," *Bull. et. mem. de Hosp. de Paris*, 53:1482, 1929.
8 Yater, W. M.: "Cyst of Pericardium," *Am. Heart J.*, 31:6, 1930.

9 Stoerk, H.: "A Case of Endothelioma Developing on the Pericardium," *Ann. d'anat. path.*, 16:660, 1935.
10 Skinner, G. F. and Hobbs, M. E.: "Intrathoracic Cystic Lymphangioma," *J. Thoracic Surg.*, 6:98, 1936.
11 Cushing, E. H.: "Diverticulum of Pericardium," *Arch. Int. Med.*, 59: 56, 1937.
12 Churchill, E. D.: "Simple Cyst of the Mediastinum," *New Eng. J. Med.*, 217:958, 1937.
13 Haas, L.: "Diverticulum Pericardi," *Acta radiol.*, 20:228, 1939.
14 Lambert, A. V.: "Etiology of Thin-Walled Thoracic Cysts," *J. Thoracic Surg.*, 10:1, 1940.
15 Curreri, A. R. and Gale, J. W.: "Mediastinal Cysts," *Ann. Surg.*, 113: 1086, 1941.
16 Greenfield, L., Steinberg, I. and Touroff, A. S. W.: "Spring Water Cyst of the Mediastinum," *J. Thoracic Surg.*, 12:495, 1942.
17 Laipply, T. C.: "Cysts and Cystic Tumors of the Mediastinum," *Arch. Path.*, 39:153, 1945.
18 Kinsella, T. J.: "Thoracic Tumors," Philadelphia, 1945.
19 Blades, B.: "Mediastinal Tumors," *Ann. Surg.*, 123:749, 1946.
20 Maser, M. L.: "True Pericardial Diverticulum," *Am. J. Roentgenol. and Rad. Therapy*, 56:27, 1946.
21 Lam, C. R.: "Pericardial Celomic Cysts," *Radiology*, 48:239, 1947.
22 Bradford, M. L., Watson, H. W. and Grow, J. B.: "Mediastinal Cysts and Tumors," *Surg., Gynec. and Obst.*, 85:467, 1947.
23 Leahy, L. J. and Culver, G. J.: "Pericardial Coelomic Cyst," *J. Thoracic Surg.*, 16:695, 1947.
24 Schein, C. J.: "Cyst of the Pericardium," *Am. J. Surg.*, 78:411, 1949.
25 Craddock, W. L.: "Cysts of the Pericardium," To be published, *Am. Heart J.*, 1951.

A Case of Plasmacytoma of the Lung*

M. KULEY, M.D. and O. KUNTMAN, M.D.
Istanbul, Turkey

The patient, M.A., is a 30 year old housewife who for the last five years, has complained of pain in the back which suddenly increased in intensity two months previous to her admittance to the hospital, at first, with chills, later with fever, coughing and dark colored sputum. Within a few days the pain in her back decreased in intensity but as the fever, coughing and expectoration continued, she was admitted to the hospital on December 1, 1947.

In her past history there was nothing of significance except malaria. Physical examination revealed the circulatory, digestive and nervous systems to be normal, but, examination of the respiratory system showed an increase in vocal fremitus, dullness and large moist rales in the right paravertebral region at the level of the scapula.

Roentgenologically, at the right, a homogenous tumour-like density was detected lying along the right boundary of the heart, and the outer border of which was fairly even and rounded (Fig. 1). The amount of yellowish green sputum was 25 to 100 cc. per 24 hours, with plenty of leucocytes but no acid-fast bacilli, elastic fibers or hooks. At the time of her admission, once only, were found 3.5 grams albumin per litre urine.

She stayed at the hospital from December 1, 1947 until April 4, 1948, and was treated with penicillin and sulphonamides. Her general health improved somewhat, sputum decreased and she gained in weight (former weight 59 Kg., after treatment 62 Kg.).

On January 25, 1949 she applied for admission for the second time, complaining of fever, pain in the right side and bloody sputum which sometimes had a foul odor.

Roentgenological inspection of the lung showed a small clearing in the upper section of the tumor-like density seen in the right hilus. When an aspiration biopsy was carried out behind a fluoroscopic screen, the needle passed through a hard and resistant structure, then through a softer one. In a smear prepared from the contents of the needle were seen reticulum cells, lymphocytes, polymorph leucocytes and about 70 per cent plasma cells. Because of the great percentage of plasma cells a sternal marrow aspiration was made. In the myelogram 4 per cent plasma cells were detected. No plasma cells were seen in the aspiration biopsy made from the liver and the spleen. Nor were any plasma cells seen in the blood.

In this case the large amount of sputum and the clearing seen in the tumor-like density led us to suspect a chronic suppurative disease of the lung, but, as no elastic fibers could be detected in repeated examinations of the sputum, we accepted this suppuration to originate from a chronic bronchial disease and this plasma-cell homogenous infiltration to be a granular plasma-cell tumor.

*From the Istanbul University Medical School, Department of Medicine, Ord. Prof. Tevfik Saglam.

FIGURE 3

FIGURE 2

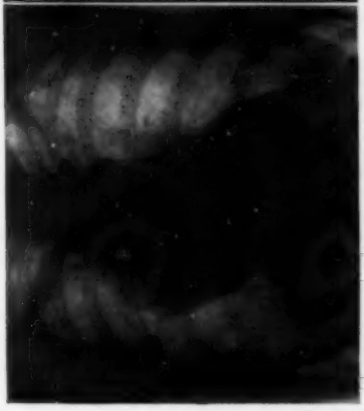


FIGURE 1

Discussion

Cases of extramedullar plasma-cell tumor are but rarely seen in clinics. Since it first became a subject of study, the number of cases published is less than 150. The clinical diagnosis of these cases, localization, their histological structure, origin of the cells, their being accepted as a tumor or a systemic disease, and their relation to myeloma and plasma-cell leukemia has drawn the attention of many authors.

Extramedullary plasmacytoma is found in the upper respiratory tract, the digestive tract and the jejunum, and more especially in the soft regions of the body, rarely in the thyroid gland and the pleura. It is usually single but may, sometimes, be multiple. Its size varies. They may be oval or round in shape. They are often benign and not ulcerated. They are localized and do not lead to metastasis; except in rare cases when they cause metastases in the regional lymph glands, or still more rarely in the bones.

Plasmocytomas, from the histological point of view, sometimes consist of plasma-cells only and have the appearance of a real primary tumor. This type can be classified as plasma-cell tumors (Schridde, Werdt, Menzel, Thibaudeau, Mathz and Bolt). While, in some other plasmocytomas, the tumor is constructed mainly of plasma cells, ample lymphocytes, leucocytes and fibroblasts are also found. It is preferable to differentiate this latter form from the tumoural type and to consider it as a plasma-cell granuloma (Hedinger, Kaufmann and Voegt). These often occur around a focus of infection. In fact, the relationship between infection and inflammatory processes and the development of plasma-cells has long been known. Moreover, in chronic infections, in severe sepsis, diseases of the lung, rheumatism, lymphogranulomatosis and in some mycotic infections a plasmacellular reaction up to 60 per cent may be seen. And, sometimes, it may be difficult to differentiate these cases from myeloma.

The plasma cells seen in plasmacytomas are similar to myeloma cells. Their cytoplasm shows strong basophilia, their nuclei are excentric and round like cart-wheels. A change takes place in the staining of the cytoplasm, and sometimes vacuoles are formed according to the cell's individual function and to the course of the disease. But the cells in myeloma are younger, larger and show a stronger basophilia.

There is a difference of opinion among authors as to the origin of the plasma cells in extramedullary plasmacytoma and those in myeloma. Some authors have suggested that the plasma cells in myeloma originate from myeloid reticuloendothelial cells (Rohr, E. S. Egeli and his collaborators). Others accept the theory that

myeloma cells originate from the young myeloid cells in the bone marrow (Scheele, Herxheimer). Aschoff speaks of plasma-cell hyperplasia in the lymph nodes and the difficulty in determining whether it is a tumor or a granuloma. Aschoff and Klemperer maintain that sometimes the plasma cells have a lymphocytic or lymphoblastic origin and call these cells "lymphoblastic and lymphocytic myeloma cells." But Zadek thinks it better to call these cells "lymphoid plasma cells." Marschalko accepts the mononuclears which possess the power of defence as stem-cells of the plasma cells. Klima believes the plasma cells to be a special type of cells, and, like all other blood cells, to originate from undifferentiated mesenchyme cells. Askanazy assumes that plasma cells have more than one origin. Moeschlin demonstrated, in a series of lymph node preparations in cases of German measles, young, large plasmoblasts and their forms of development and the typical plasma cells. However, in these cases plasma cells are not seen in the circulating blood, and it is only in the regions of the bone marrow, where lymphatic tissue is found that plasmoblasts and plasmacytes have been encountered in the myelogram. These cells, which are different from lymphoblasts and lymphocytes, are claimed to have originated from the reticuloendothelial system in the lymphatic tissue. Despite the different results obtained in studies based on the origin of plasma cells, it is now generally accepted that, whether these cells originate from the myeloid tissue in the myeloma or from lymphatic tissue in the primary extramedullary plasmacytoma and other inflammatory diseases, the stem cells in either case are the same reticuloendothelial system cells (Rohr, Morkoff, Nordenson, Schmitten, Zadek).

In extramedullary plasmacytoma as in myeloma there is detected, in the blood, an increase of globulin due to the specific secretory function of plasma cells (Magnus-Levy, Hans, Klima, Rohr, Umdritz, Henning, Fleischhacker). This increase in the globulin formation upsets the protein balance of the blood. Tests, such as Takata-Ara, the cadmium reactions, the Weltmann lines give positive results. In severe cases, almost no change in the sedimentation rate can be detected, and the cadmium reaction is but slightly positive. With our patient, the Takata-Ara and the cadmium reactions were positive, and the sedimentation rate showed an increase of 8-20-40, and the general health of the patient showed that the course of the illness was not hopeless.

Although a difference between the albumin formation of the plasma cells originating from the bone marrow and that of the reticuloendothelial tissue in the lymphatic system has been given some consideration, the reticuloendothelial system being the origin in both cases, the occurrence of hyperglobulinemia cannot be re-

jected in either. Similarly, even though our case is an extramedullary plasmacytoma originating from the lymphatic system, it shows a marked paraproteinemia and hyperglobulinemia.

Furthermore, the young and atypical plasma cells are valuable in determining histologically the character of the plasmacytoma. If the cell is young and atypical, the prognosis is always severe. The type of cell in our case being mature, a good prognosis is confirmed once again.

In many of these cases, the metabolism is upset. A simple cloudy swelling in the kidneys, hyaline degeneration in the epithelial cells, and disturbance in the tubules are seen. Bence-Jones albumin is detected in the urine (Apitz). Occasionally, in the advanced stages of the disease, anuria appears, due to the mechanical occlusion in the tubules. Though there is no disturbance in the glomeruli, the advanced stages of the disease, tubular atrophie, cortical sclerosis and renal insufficiency occurs progressively. This disease is a special type of the nephrotic syndrome and, at first, a retention, and later, a hydronephrosis develop. These cases are known as nephrohydrosis, and can be considered as a renal disturbance resulting from humoural changes (Tannhauser, Randeratt). Bence-Jones albuminuria has been claimed to be a product of the chemical changes of the plasma cells. But the occurrence of cases which show Bence-Jones albuminuria despite the lack of plasmocytoma, makes it better to explain the fact as a paraproteinemia. Only once in our case have we detected albuminuria; in the subsequent urine examinations neither has albuminuria nor has an insufficiency of the renal function been found. In the above mentioned cases there is a paraamyloid degeneration (first detected by Magnus-Levy). Paraamyloidosis is different from other amyloid degeneration. Amyloidosis occurs usually in the kidneys, the liver, the spleen and around the endothelium of the blood vessels. Paraamyloidosis occurs especially in the striated muscles, the bones, the lungs and around the joints and mesenchymal tissues.

The relationship between cases of extramedullary plasmacytoma and myeloma or plasma-cell leukemia has drawn the attention of many authors and has led to a number of discussions. Although they have some clinical features in common, regardless of the fact whether the plasmacytoma is a granuloma of an inflammatory origin or a primary tumour, they begin as a localized disease. In plasmacytoma, no plasma cells are seen in the periferal blood. Plasmacytoma usually originates from the reticuloendothelial tissue of the lymphatic system. While myeloma is a systemic disease and originates from the reticuloendothelial cells in the myeloid system. The plasma cells in myeloma are large and young. Even in the early stages, plasma cells are seen in the capillary blood, and

cause metastasis in the liver, the spleen and the lymph nodes.

Plasma-cell leukemias show a diffuse character and a hiatus in the development of the cells and a metastasis in all the organs. Contrary to myeloma, they never develop into tumors. Anemia and neutropenia occur. They usually take an aleukemic course. Although there is ample localization in myeloma, the blood and other organs, infiltrations are greater in plasma-cell leukemia. However, in some cases of myeloma there may be seen an extramedullary plasmacytoma in the form of a metastasis; in some cases of plasmacytoma a metastasis in the skeletal system may also be seen. Plasmacytoma is essentially benign in nature, but, it may become malignant.

Therefore, the answer to the question whether plasmacytoma is a systemic disease or a tumor is difficult to give. These three forms may change from the one into the other. In some of these cases the tumor has a capsule and it can be removed by operation. Cases where the tumor can not be removed are very sensitive to roentgen-ray therapy.

Sulphonamides and penicillin were administered to our patient to counteract the large amount of sputum, while, on the other hand, the patient was submitted to radiation therapy: 37 treatments with 150 r, 18 with 200 r, a total of 9,150 r. The patient who weighed 45 Kg. at the start put on weight and weighed 75 Kg. after the treatment. The temperature fell to its normal level, the sputum stopped, the tumoural density as seen in the x-ray films almost disappeared (Figs. 2 and 3).

Summary: A case of plasmacytoma is discussed.

Resumen: Se discuta un caso de plasmacytoma.

Resumé: L'auteur discuté une cas de plasmocytoma.

REFERENCES

Askanazy, M. and Dubois-Ferriére, H.: "La cellule plasmatique et la leucémie plasmacellulaire," *Helvetica med. Acta*, 9:427, 1942.
Apitz, K.: "Die Paraproteinosen, Ueber die Storung des Eiweisstoffwechsels bei Plasmocytom," *Virchow's Archiv.*, 306:634, 1940.
Cappell, D. F. and Mathers, P.: "Plasmacytoma of the petrous temporal bone and base of skull," *J. Laryngol.*, 50:340, 1935.
Chesterman: "Solitary plasmacytoma of the long bones," *British J. Surg.*, No. 140, P. 440, 1948.
Ekrem Serif Egeli, Sermet Ergun ve Ilhan Ulagay: "Bir miyelom vakasi münasebetile," *Turk. Tib Cemiyeti mecmuasi*, 1947.
Jaeger, E.: "Das extramedullare Plasmocytom," *Zeitschrift für Krebsforschung*, 52, 1942.
Ferranda, Salvatore and Goidotti, Carlo: "Beitrag zum Studium des solitaren plasmazellen myeloms des Oberschenkels beim Erwachsenen," *Chirurgie und ihre Grenzgebiete*, 108, 1943.
Figi, F. A., Broders, A. C. and Havens, F. Z.: "Plasma cell tumors of the upper part of the respiratory tract," *Ann. Otol., Rhinol. and Laryngol.*, 54:283, 1945.
Fleischhacker, H. and Klima, R.: "Beitrag zur Kenntnis des multiplen

Myeloms, der plasmacellularen Leukaemie und des plasmacellularen Granuloms," *Folia Haematologica*, 56:5, 1936.
Fleischhacker, H.: "Uber die Plasmazellen und das reticuloendotheliale System des Knochen markes," *Deutsches Archiv für klinische Med.*, 186: 506, 1940.
Lumb, G.: "Solitary plasmacytoma of bone with renal changes." *Brit. J. Surg.*, 36:141, 1948.
Hefferman: "Plasmocytom des Pankreas und Duodenum mit ileus," *Schweizerische med. Wchachn.*, 78:142, 1948.
Hans Voegt: "Extramedullare plasmacytome," *Virchows Archivs*, 302: 497, 1938.
Jeney, A.: "Eine Abstammungslehre der Lymphocyten, als Grundlage für Analysierung der Blut veranderungen und Bluterkrankungen," *Klinische Wchschr.*, 15:718, 1936.
Jores, A and Bruns, W.: "Ein Fall von 'malign Plasmom' wit einem Beitrag zur sog, Plasmazellenleukamie," *Folia Haematologica*, 55:227, 1936.
Bross, K.: "Zur Plasmozytomfrage," *Folia Haematologica*, 45:137, 1931.
Blumenfeld, L.: "Plasma cell tumor of the nose and nasopharynx," *Ann. Otol., Rhin., and Laryng.*, 45:436, 1936.
Marshal, G. and Mallet: "La plasmocytose concéreuse," *Le Sang*, 7:457, 1948.
Mattick, W. L. and Thibaudeau, A. A.: "Extramedullary plasma cell tumors of the upper air passages," *Am. J. Cancer*, 23:513, 1935.
Moeschlin, S.: "Untersuchungen über Genese und Funktion der Blutplasmazellen anhand von Lymphdrüsen und Sternalpunktaten bei Rubeolen," *Helvetica Med. Acta*, 7:287, 1940.
Wiss and Vandory: "Uber zwei Falle von Plasmacytom im Kieforknochen," *Zeitschrift für Stomatologie*, 24:39, 1941.

Obstructions of Superior Vena Cava

L. H. FERGUSON, JR., M.D. and Wm. A. WERNER, M.D.*
St. Louis, Missouri

Obstructions of the superior vena cava whether partial or complete are rare clinical, surgical and pathological entities. Thrombosis resulting from injury, usually of an indirect nature to the superior vena cava, is probably the etiological agent. The clinical manifestations which alarm the patient are a gradually developing edema of the upper half of the body especially the face, the tortuous, distended veins of the chest and neck, and cyanosis of the lips and lobes of the ears. The symptoms will be modified or exaggerated depending upon the location of the lesion in relation to the vena azygos which may in certain instances partially take over the function of the superior vena cava. The prognosis depends upon the rapidity in the formation of adequate collateral circulation and surgical eradication of the obstructing mass.

Case Reports

Obstruction Above the Orifice of the Vena Azygos, Case 1: This man of 45 years, a mechanic, entered the hospital complaining of swelling of face and eyelids, lacrimation and distended veins of neck, chest and abdomen. Twelve months previous to admission he developed bilateral swelling of the neck believed to be due to adenitis. He was treated and in two or three weeks the face began to swell and the veins of the chest became distended. He was able to walk or run without difficulty but his work or excitement seemed to aggravate the condition. His family and regional history were non contributory. Physical examination revealed a well developed male in no acute distress. The face was flushed, swollen but no pitting edema was present. His chest was symmetrical, respiratory excursion equal, 20/min., and the percussion notes and tactile fremitus were equal. No rales were detected. The cutaneous vessels were dilated and tortuous, especially in the neck, and radiating medially from the axilla. There was a tortuous tender vein to the right of the sternal border. The superficial epigastrics were markedly distended but not tender. The heart rate, 80 per minute, was of good quality. No detectable enlargement or murmurs were present. Blood pressure was 122/72 left arm, 120/68 right arm and 120/80 right leg. The abdomen, skin, extremities, neurological findings, ear, nose and throat were within normal limits. X-ray film inspection of the chest was normal.

Urine with specific gravity of 1.004, and acid, contained no sugar, al-

*From St. John's Hospital, St. Louis, Missouri.
Surgical Service: J. L. Mudd, M.D.
L. H. Ferguson, M.D., Surgical Resident.
Medical Service: J. J. Hammond, M.D.
Wm. A. Werner, M.D., Medical Resident.
Pathology Department: Hollis N. Allen, M.D.

bumen, casts, red or white blood cells. There were no abnormal blood findings.

Right exploratory thoracotomy was performed and a tumor mass about two inches long and one inch in diameter was found just above the greatly dilated vena azygos. The tumor mass involved the lumen of the superior vena cava and apparently completely obstructed it. Due to the size and extensiveness of the tumor, we felt that the risk involved in removing it was too great to warrant the attempt. The chest wall was reconstructed in layers. Postoperative course was uneventful for seven days, when the patient became nervous; pulse rapid, irregular and weak. He was perspiring profusely but wasn't complaining of pain. Sodium luminal and quinidine were administered and within 72 hours the pulse was regular.

E.K.G. revealed evidence of paroxysmal supraventricular tachycardia (initial tracing. Forty eight hours after initial tracing the E.K.G. indicated myocardial pathology, right axis deviation (slight) and sinus mechanism restored. X-ray inspection of the chest showed evidence of a slight amount of fluid in the base of right pleural space and apparently some air was also present. The chest otherwise appeared clear.

Obstruction Occluding the Orifice of the Vena Azygos, Case 2: This 27 year old housewife entered the hospital complaining of flushing of face and neck and enlarged veins on surface of the chest. One and one half years ago she noticed her face became flushed when her hands were raised above her head. Within two or three months the veins of the chest and abdomen became large and prominent. During the past two months her face was swollen only in the morning. The slightest exertion or emotional activity caused a feeling of severe pressure in the neck and the face became flushed. Recently she noticed some swelling of her hands at night. Past, family and regional history were non contributory.

Physical examination revealed a well developed, well nourished white female in no acute distress. Her face was flushed and swollen and a hard subcutaneous nodule was present in left posterior triangle of the neck. Many dilated tortuous veins were present over the chest and abdomen that seemed to be anastomosing frequently with the inferior epigastric vessels. Her chest was symmetrical and the voice and breath sounds clear. The precussion notes were normal and no rales were present. The apex of the heart was in the fifth interspace, three and one half inches from the midsternal line. The rate was 88 per minute. The tones were normal and there were no murmurs. Her blood pressure was 122/74. The abdomen was normal except for large dilated veins. The urine was negative except for a trace of albumen and occasional blood cells. No significant abnormality was found in the blood.

Exploratory thoracotomy revealed a tumor mass involving the superior vena cava at its junction with the azygos vein. The tumor extended superiorly one and one half inches and inferiorly below the azygos about one fourth inch. The superior intercostal veins as well as these from the internal mammary were greatly enlarged. The phrenic nerve was also involved in the mass. There were several small adhesions between the lung and chest wall. The superior vena cava above the obstruction was not particularly enlarged and neither was the vena cava below the tumor. The tumor mass was freed from the surrounding structures. The vena azygos, the vessels from the internal mammary and the superior vena cava above and below the mass were ligated. The phrenic nerve was severed and the tumor separated from the surrounding structures and

removed. The chest wall was reconstructed in layers. Drainage was established by means of a trocar and catheter in the posterior axillary line. Postoperative course was uneventful and she was discharged on the 12th day.

On March 1, 1948 x-ray inspection of the chest showed a collection of fluid and air in the right pleural space with a resection of the anterior portion of the fourth rib. There was a catheter in the right chest draining the fluid. The left chest was clear.

Pathological report by Dr. H. N. Allen: *Gross:* Specimen consists of tissue representing about 20 mm. of the superior vena cava. Surrounding the vessel there is a fibrous tissue nodule about 30 mm. in diameter rather irregular in outline which is nearly completely obliterating the vessel. Towards one edge and just on the exterior of the vessel there is a calcified nodule about 10 mm. in diameter which is breaking down. The tissue is hard and very tough. It does not have the appearance of malignancy. Second specimen consists of lymph nodes highly pigmented, apparently from anthrocosis.

Microscopic: Section shows hard fibrous tissue containing areas of large endothelial like cells. These cells are extending in cord like formation out between the fibrous tissue and in areas form solid masses and whirls. The cells are not hyperchromatic and show no mitotic figures, seems to be part of the general inflammatory reaction. There is no evidence of malignancy that can be seen in these sections.

This is apparently a fibrous reaction possibly secondary to the granuloma causing the calcified node, and possibly the result of organization of an old thrombus of the vena cava.

SUMMARY

A report of two cases of obstruction to the superior vena cava.

RESUMEN

Se discuta dos casos de obstrucción de la vena cava superior.

RESUME

L'auteur rapporte deux cas d'obstruction d'elle vena cava supérieure.

REFERENCES

1 Ochsner, Alton and Dixon, J. L.: "Superior Vena Cava Thormbosis," *J. Thor. Surg.*, 5:641, 1936.
2 Ehrlich, William, Ballon, Harry C. and Graham, Evarts A.: "Superior Vena Caval Obstruction with a Consideration of the Possible Relief of Symptoms by Mediastinal Decompression," *J. Thor. Surg.*, 3:352, 1934.
3 Gray, Howard K. and Skinner, Ira C.: "Constrictive Occlusion of Superior Vena Cava," *Surg., Gyne. and Obst.*, 72:923, 1941.
4 Fischer (Quoted by Ehrlich, William, Ballon, Harry C., Graham, E. A.).
5 Lion, C. and Aboya, A. (Quoted by Ochsner and Dixon).
6 Carlson, H. A.: "Superior Vena Cava Obstruction," *Proc. Sec. Exp. Biol. and Med.*, 30:293, 1932.

Seventeenth Annual Meeting of the College

The Seventeenth Annual Meeting of the American College of Chest Physicians will be held at the Ambassador Hotel, Atlantic City, New Jersey, June 7 through 10, 1951. The One Hundredth Annual Session of the American Medical Association will take place in Atlantic City, June 11-15, 1951. Reservations at the Ambassador Hotel for the College meeting and the American Medical Association session may be made by writing directly to the hotel and it is suggested that reservations be made at once. It is essential to mention the American College of Chest Physicians meeting when writing for reservations. Deposits are required from those physicians planning to remain for the American Medical Association meeting.

The scientific program to be presented at the annual meeting is now in preparation. The members of the Committee on Scientific Program are: Dr. Edwin R. Levine, Chicago, Illinois, chairman; Dr. Alvan L. Barach, New York City; Dr. Paul H. Holinger, Chicago, Illinois; Dr. Richard H. Overholt, Brookline, Massachusetts; Dr. Leo G. Rigler, Minneapolis, Minnesota; and Dr. Harold G. Trimble, Oakland, California. Physicians are invited to submit titles and abstracts of their material to Dr. Edwin R. Levine, chairman, 109 North Wabash Av., Chicago, Ill.

The annual x-ray conference will be presided over by Dr. Rigler and is scheduled to be held on Saturday afternoon, June 9. Physicians who plan to attend the meeting are invited to submit interesting or unusual proved cases for demonstration and discussion. Films must be of good quality and the examination complete. Please send films, together with clinical abstract and laboratory findings of the case, to Dr. Leo G. Rigler, University of Minnesota Hospitals, Minneapolis 14, Minnesota for consideration.

Dr. Holinger of Chicago is in charge of the motion picture session on diseases of the chest to be presented on Friday evening, June 8. Physicians who wish to present a motion picture film at the session kindly send title and description of film, the size of the film, whether silent or sound, color or black and white, to Dr. Paul H. Holinger, 700 North Michigan Avenue, Chicago, Illinois.

Dr. Harold G. Trimble of Oakland, California, will supervise the organization of the round table discussions. These popular sessions are being planned for Friday, Saturday and Sunday, June 8, 9 and 10. Suggestions for subject matter should be forwarded to Dr. Trimble, 2930 Summit Street, Oakland, California.

Minutes of the Semi-Annual Meeting Board of Regents

The Semi-Annual Meeting of the Board of Regents of the College was held at the Statler Hotel, Cleveland, Ohio, on Monday, December 4, 1950. The meeting was called to order by Dr. James H. Stygall, Chairman, at 2:00 p. m. The following Officers, Regents and invited guests were present at the meeting:

James H. Stygall, Indianapolis, Indiana, Chairman
Russell S. Anderson, Erie, Pennsylvania
Andrew L. Banyai, Milwaukee, Wisconsin

Otto L. Bettag, Chicago, Illinois
Benjamin L. Brock, Downey, Illinois
Martin H. Collier, Blackwood, New Jersey
Everett F. Conlogue, Dayton, Ohio
Alfred Goldman, St. Louis, Missouri
Burgess Gordon, Philadelphia, Pennsylvania
Alvis E. Greer, Houston, Texas
Charles M. Hendricks, El Paso, Texas
Chevalier L. Jackson, Philadelphia, Pennsylvania
Hollis E. Johnson, Nashville, Tennessee
William A. Hudson, Detroit, Michigan
Edward Lebovitz, Pittsburgh, Pennsylvania
Edwin R. Levine, Chicago, Illinois
Louis Mark, Columbus, Ohio
Donald R. McKay, Buffalo, New York
Jay Arthur Myers, Minneaoplis, Minnesota
William E. Ogden, Toronto, Canada
Joseph C. Placak, Cleveland, Ohio
William R. Rumel, Salt Lake City, Utah
Murray Kornfeld, Chicago, Illinois, Executive Secretary
Harriet E. Lumm, Chicago, Illinois, Assistant Secretary

A resolution was presented concerning the publication of a new College Directory:

"WHEREAS, The last roster of the College membership was published at the beginning of 1948, and

"WHEREAS, There are 2274 members listed in the roster, and

"WHEREAS, There are at the present time 3381 members, an increase of 1107,

"THEREFORE BE IT RESOLVED, That the Board of Regents of the College authorize the publication of a new College Directory listing all members of record, together with their hospital and teaching affiliations, and

"BE IT FURTHER RESOLVED, That the Directory be sold to the members at cost, provided the order is accompanied by a check or money order in advance of the date fixed for publication; thereafter the sale price of the Directory to be increased and placed on sale to everyone desiring to purchase a copy."

The above resolution was moved for adoption by Dr. Placak, seconded by Dr. Jackson and unanimously carried.

A proposal to study the possibilities of purchasing a building in Chicago for the College was introduced by Dr. Banyai. Upon the recommendation of the Executive Council a committee comprised of Drs. Banyai, Brock and Bettag was appointed and given the authority to purchase a building with the proviso that it did not jeopardize the financial structure of the College. The Executive Council recommended that Dr. Louis Mark, President of the College, be present at all meetings concerning the purchase of a College building.

In the absence of Dr. J. Winthrop Peabody, chairman of the Committee on Board Certification, Dr. Mark discussed the matter of board certification for chest specialists and recommended that the College be represented at the meeting of the Advisory Board for Medical Specialties to be held at the Palmer House, Chicago, on February 11. This recommendation was approved upon motion of Dr. Hudson, seconded by Dr. Johnson.

Dr. Anderson, chairman of the Council of Tuberculosis Hospitals of the College, reported that the standard for tuberculosis hospitals drawn up in cooperation with the American College of Surgeons will appear in the new manual on hospital standardization which is published by them. Dr. Anderson also reported that he had, upon invitation from the American College of Surgeons, commented on the new standard for tuberculosis hospitals at the Boston Clinical Congress of the College held October 23-27, 1950. The standard for tuberculosis hospitals has been prepared in printed form and reprints may be obtained by writing to the Executive Offices of the College in Chicago.

The report of the Council on Postgraduate Medical Education was presented outlining the dates and places of postgraduate courses in diseases of the chest sponsored by the College in the past as well as those planned for the year 1951. A comparison of enrollments was included in the report.

POSTGRADUATE COURSES

City	1948	1949	1950	1951
Philadelphia	62	44	51	March 26-30
Chicago	44	38	51	To be announced
New York	76	86	107	November 12-16
Minneapolis	..	28	..	To be announced
Nashville	..	..	..	January 22-27
San Francisco	43	71	..	February 13-17
Milwaukee	..	..	..	April (4 weeks)
TOTALS	225	267	209	

Dr. Johnson reported on the postgraduate course being presented at Vanderbilt University Medical School in Nashville in January. Dr. Jackson announced the plans for the annual postgraduate course to be presented in Philadelphia in March. He stated that new speakers were being introduced in the program this year and that the final program would be available in a short time. Dr. Banyai reported on the postgraduate course for general practitioners which has been scheduled to be held in Milwaukee in April under the sponsorship of the College in cooperation with the Wisconsin Chapter of the American Academy of General Practice. He stated that the course is to be presented in lecture, clinic and demonstration form on four consecutive Wednesday afternoons during April at the auditorium of the Milwaukee Children's Hospital. The course has been granted sixteen hours of formal credit towards postgraduate education requirements of the Wisconsin Chapter of the American Academy of General Practice.

Dr. Mark recommended that the Board of Regents request the Council on Postgraduate Medical Education to study the College program of postgraduate courses and prepare a report containing specific suggestions for future plans regarding the number and management of the courses to be sponsored by the College. This recommendation was adopted upon motion by Dr. Hudson, seconded by Dr. Rumel.

Dr. Ogden commented on the very favorable reports he had received from physicians in Canada who had attended the various postgraduate courses presented in the United States.

Dr. Hendricks presented a report of the Committee on College By-Laws in which the following changes were recommended:

ARTICLE III, Section 7, (1), (2)

Line 5, reading "Sections 3 or 5 of this Article" should read "Sections 3 or 4 of this Article."

ARTICLE V, Section 10

The last sentence, reading "No agreement entered into by the Board of Regents for the services of an Executive Secretary may be of more than three years' duration" to read "No agreement entered into by the Board of Regents for the services of an Executive Secretary may be of more than ten years' duration."

ARTICLE VII, Section 3

Present wording:

Section 3: Dues shall be payable on January 1 of each year and shall become delinquent if not paid by July 1 of that year. A member who is delinquent in his dues automatically loses all privileges of the College including subscription to the official publication. A member whose dues are delinquent shall be notified of such delinquency by a regular letter, and on September 1 he shall be notified by a registered letter with return receipt requested. The notification shall contain formal notice that the member is delinquent in the payment of his dues and that if the dues are not paid by December 31 of that year, he will be dropped from the rolls of the College. If the dues are not paid by December 31, one year from the time his dues become payable, the member shall be dropped from the rolls by order of the Board of Regents.

Recommended wording:

Section 3: Dues shall be payable on January 1 of each year and shall become delinquent if not paid within sixty days thereafter. A member who is delinquent in his dues automatically loses all privileges of the College. A member whose dues shall be delinquent for a period of one year may be dropped from the roll of the College by action of the Board of Regents, and the Chairman of the Board of Regents shall notify such member by registered letter of such action by the Board.

ARTICLE X, Section 4 (b)

It is recommended that the name of the "Council on African and Near East Affairs" be changed to "Council on African and Eastern Affairs."

ARTICLE X, Section 6

It is recommended thit the "Committee on College Essay" be added to the list of standing committees.

ARTICLE XII, Section 7

It is recommended that the following paragraph be added to this section:

Dues shall be payable on January 1 of each year and shall become delinquent if not paid by July 1 of that year. A member who is delinquent in his dues automatically loses all privileges of the College. A member whose dues shall be delinquent for a period of one year may be dropped from the roll of the College by action of the Board of Regents, and the Chairman of the Board of Regents shall notify such member by registered letter of such action by the Board.

The recommendations for changes in the College By-Laws were approved by the Board of Regents upon motion by Dr. McKay, seconded by Dr. Jackson. These By-Laws will be voted upon by the membership of the College at the administrative session of the annual meeting in Atlantic City on June 9, 1951.

At the annual meeting of the College in San Francisco in June 1950, a resolution was adopted by the Board of Governors at their meeting on June 22, recommending that the qualifications for the admission of new Fellows be clarified. The resolution was presented to the Board of Regents at their meeting on June 25 and was referred by them to the Committee on Membership. At the semi-annual meeting of the Board of Regents held in Cleveland on December 4, Dr. Jackson, Chairman of the Committee on Membership, reported that his committee had studied the recommendation of the Board of Governors and was recommending to the Board of Regents that the proposal be given favorable consideration. Upon motion by Dr. Placak, seconded by Dr. Bettag, the report of the Committee on Membership was adopted.

Dr. Greer, chairman of the Board of Examiners, discussed the matter of examinations for Fellowship in the College. He recommended that in grading the examination papers, the medical and surgical questions comprise sixty per cent of the total and that anatomy, pathology, bacteriology, physiology and immunology the remaining forty per cent. This recommendation was approved by motion of Dr. Rumel, seconded by Dr. Placak.

Dr. Levine, chairman of the Committee on Scientific Program, outlined the plans for the program to be presented at the annual meeting of the College in Atlantic City, June 7 through 10, 1951. He informed the Board that a number of symposiums on various subjects are being planned in addition to the usual scientific papers, x-ray conference, round table discussions, motion pictures and other material.

It was recommended, at this point, that notices stressing the importance of early completion of hotel reservations for College members planning to attend the annual meeting in Atlantic City be released by the Executive Offices of the College at the earliest possible date.

Dr. Banyai, chairman of the Council on European Affairs, presented the report of the council. He stated that the First International Congress on Diseases of the Chest held in Rome in September of 1950 under the sponsorship of the College, attracted a tremendous amount of interest as shown by the excellent registration of nearly one thousand delegates from forty countries. Dr. Banyai pointed out that there was a one hundred per cent membership increase in Europe during 1950. This was, in a large measure, due to the Rome Congress and the publicity concerning the Congress.

A preliminary report from Dr. Milton I. Levine, New York City, representing the College at the Midcentury White House Conference on Children and Youth, was read. Dr. Levine pointed out how the College could be of assistance to the Conference. Included in his report were a number of recommendations whereby the treatment and care of children suffering from chest disorders might be improved. Dr. Levine indicated that a complete report of the Conference would be submitted at an early date. Upon motion by Dr. Mark, Dr. Levine's report was approved with the sincere appreciation of the Board of Regents.

Announcement was made of the organization of the forty-first chapter of the College. The North Carolina Chapter, No. 41, was organized at Oteen on November 24, 1950, and a scientific program was presented in connection with the organizational meeting. The meeting was held at the Veterans Administration Hospital at Oteen.

Dr. Banyai, chairman of the editorial committee for the book on nontuberculous diseases of the chest, presented a report concerning the book

which is being sponsored by the Council on Undergraduate Medical Education of the College. The manuscript for the book, Dr. Banyai reported, was now in the hands of the publisher and early publication is anticipated.

The Journal of the Kentucky State Medical Association devoted a full page in their November 1950 issue to comment on the activities of the Kentucky Chapter of the College. The Board of Regents passed a resolution expressing their appreciation to the editor of the journal for this excellent article and recommended that the editors of other state medical journals be contacted by the chapter officials in their respective states and districts for such publicity.

Announcement was made of the article concerning the teaching of diseases of the chest in the medical schools prepared by Dr. Edward W. Hayes, Monrovia, California, chairman of the Council on Undergraduate Medical Education of the College, who was unable to be present at the Board meeting. It was reported that Dr. Hayes' article was to appear in an early issue of the Journal of American Medical Colleges. The Board of Regents recommended that reprints of the article be obtained for distribution by the College to interested physicians.

A brief talk was presented by Dr. Mark, welcoming the return of Dr. Ogden to the Board meetings after his illness last winter. Dr. Ogden responded by stating that it was a great pleasure for him to be able to meet with his friends once again.

Following the reading of special announcements and communications the meeting was adjourned.

Meeting of the Editorial Board Diseases of the Chest

A meeting of the Editorial Board of the College journal "Diseases of the Chest" was held in Cleveland at the Statler Hotel on December 4, 1950. Those present included Dr. Jay Arthur Myers, Minneapolis, Editor-in-Chief and chairman of the Board, Dr. Andrew L. Banyai, Milwaukee, and Dr. Charles M. Hendricks, El Paso, Board members, and Mr. Murray Kornfeld, Chicago, Managing Editor of the journal.

The following recommendations were discussed and approved by the Board:

Beginning with the January 1951 issue of "Diseases of the Chest," French summaries are to be published with each scientific paper.

Scientific papers presented at the First International Congress of the College held in Rome, September 1950, are to be published in several issues of the journal in the year 1951.

More scientific papers devoted to cardiovascular diseases and cardiac surgery are to be published in the journal.

Papers submitted for publication are to be limited to six thousand words; each page of the manuscript and all illustrations are to be properly identified by author's name and subject; bibliographies are to be prepared uniformly, in the style followed by the journal; the cost of four illustrations to be met by the journal, additional illustrations to be paid by the author; all manuscripts to be typewritten, double-spaced, with wide margins.

Committee on Nominations

Elections for offices expiring in June 1951 will be held at the Ambassador Hotel, Atlantic City, on June 9. Recommendations for elective offices may be addressed to the chairman of the Committee on Nominations, Dr. Jay Arthur Myers, 111 Millard Hall, University of Minnesota, Minneapolis 14, Minnesota. The other members of the committee are Dr. David H. Waterman, Knoxville, Tennessee, and Dr. James S. Edlin, New York City.

Prize Essay Award

The Board of Regents of the American College of Chest Physicians offers a cash prize award of two-hundred-and-fifty dollars ($250.00) to be given annually for the best original contribution, preferably by a young investigator, on any phase relating to chest disease.

The prize is open to contestants of foreign countries as well as those residing in the United States. The winning contribution will be selected by a board of impartial judges and the next award will be made at the forthcoming annual meeting of the College to be held in Atlantic City, June 7-10, 1951.

The College reserves the right to invite the winner to present his contribution at the annual meeting, and to publish the essay in its official publication "Diseases of the Chest." Contestants are advised to study the format of "Diseases of the Chest" as to the length, form and arrangement of illustrations to guide them in the preparation of the manuscript.

The following conditions must be observed:

(1) Five copies of the manuscript, typewritten in English, should be submitted to the office of the American College of Chest Physicians not later than April 1, 1951.

(2) The only means of identification of the author or authors shall be a motto or other device on the title page and a sealed envelope, bearing the same motto on the outside, enclosing the name of the author or authors.

Additional information may be obtained from the Executive Secretary of the College, 500 North Dearborn Street, Chicago 10, Illinois.

Committee on Prize Essay

Eli H. Rubin, New York City, Chairman
Charles P. Bailey, Philadelphia, Pennsylvania
Hugh L. Houston, Murray, Kentucky
David Salkin, San Fernando, California
Henry C. Sweany, Jacksonville, Florida.

TENTH ITALIAN CONGRESS OF TUBERCULOSIS

The Tenth Congress of Tuberculosis will take place in Naples, Italy, at the Institute "Principi di Piemonte" in May of 1951. Professor Vincenzo Monaldi, director of the institute, is President of the arrangements committee for the congress, and Professor Gino Babolini serves as the Secretary-General.

College Chapter News

ILLINOIS CHAPTER

The Illinois Chapter of the College held a joint meeting with the Chicago Tuberculosis Society on January 12 in Chicago. A panel discussion on chest diseases in industry was presented in which the following physicians participated: Drs. Edward C. Holmblad, Thomas C. Angerstein, Joseph H. Chivers, Lloyd E. Hamlin, Jerome R. Head and David B. Radner.

MISSOURI CHAPTER MEETING

The annual meeting of the Missouri Chapter will be held in Kansas City on Sunday, April 22. Dr. J. S. Hoffman, chairman of the program committee, has announced that the scientific program for the meeting is in preparation and that Dr. Andrew L. Banyai, Milwaukee, Wisconsin, First Vice-President of the College, will be a guest speaker.

PACIFIC NORTHWEST CHAPTER

The Pacific Northwest Chapter held its annual meeting jointly with the Pacific Northwest Trudeau Society on November 17 and 18, 1950. The meeting was held at the University of Washington School of Medicine in Seattle. A full day scientific program was presented on Friday, November 17, and a half day session on Saturday morning, November 18. At the annual business meeting of the chapter, the following officers were elected:

William S. Conklin, Portland, Oregon, President
George D. Saxton, Vancouver, Washington, Vice-President
Byron F. Francis, Seattle, Washington, Secretary-Treasurer.

SOUTH AFRICAN CHAPTER

The South African Chapter of the College held meetings in Cape Town on July 3, 1950, at the home of Dr. Theodore Schrire, and on August 1, 1950, at the home of Dr. David P. Marais. Dr. Marais, Regent of the College for South Africa, presided at the meetings.

Present at the meeting on July 3, besides Dr. Marais and Dr. Schrire, were Drs. Jacob, Landau, Nellen, Phillips, Hoole, Ackerman, Jacobson, Muller and two visitors. Dr. Marais and Dr. Schrire announced that they were planning to attend the First International Congress of the College in Rome, September 17-22, and that during their absence Dr. Walter L. Phillips would serve as chairman of the meetings. The program consisted of the presentation of case reports by Drs. Ackerman, Jacob, Muller, Marais, Schrire and Phillips.

At the meeting held on August 1, those present were Drs. Marais, Ackermann, Jacob, Nellen, Landau, Jacobson, Brauer, Hirschon, Hoole, Baumann, Meyer, Phillips and Muller. Professor Robert Goetz of the University of Cape Town was also present as well as two visitors. Professor Goetz presented cases of angiocardiography in conjunction with Dr. Nellen who had done catheter studies on the same cases. Discussion of cases presented by Drs. Muller, Jacobson and Ackermann followed.

PUERTO RICO CHAPTER

The Puerto Rico Chapter of the College held its annual meeting on December 14, 1950, together with the Section on Phtisiology of the Puerto Rico Medical Association. Drs. Jose L. Porrata, Jaime F. Pou, Pedro Domingo and David Rodriguez-Perez presented papers in the scientific program. Guest speakers were Dr. Louis H. Clerf of Philadelphia, and Dr. Frank C. Lahey of Boston.

At the business meeting of the chapter the following officers were elected for the year 1951:

E. Martinez Rivera, Rio Piedras, President
J. Soto Ramos, Rio Piedras, Vice-President
Fernando Padro, Santurce, Secretary-Treasurer.

Members of the Executive Committee are: Drs. H. Marrero Otero, Fernando Buxeda, Ramon T. Colon, Eugenio Fernandez Cerra, A. M. Marchand (Regent) and Jaime F. Pou (Governor).

College News Notes

Dr. Burgess Gordon, Philadelphia, Governor of the College for Pennsylvania, presented a paper on "The Recent Advances in the Study and Treatment of Silicosis" at the Mexican Congress on Tuberculosis and Silicosis held at San Luis Potosi, Mexico during the week of January 21-27. He also spoke at a special luncheon meeting of the Mexican Chapter of the College held in Mexico City following the congress in San Luis Potosi. Dr. Gordon will also lecture in the postgraduate course sponsored by the College in cooperation with the University of California and Stanford University Schools of Medicine to be held in San Francisco during the week of February 19 through 23. Dr. Gordon will lecture on the following subjects: "Physiologic Testing in the Diagnosis of Chronic Pulmonary Conditions," "Clinical and Physiologic Evaluations of Disability in Chronic Pulmonary Disease," "Disability Considerations in Silicosis," and "Clinical and Physiological Management of Chronic Pulmonary Diseases." On February 23 Dr. Gordon will speak before a special meeting of the College members in Southern California to be held at Cedars of Lebanon Hospital, Los Angeles. His subject will be "The Physiological Considerations in the Treatment of Chronic Pulmonary Diseases."

Dr. Alvan L. Barach, New York City, is also scheduled to lecture at the San Francisco postgraduate course. His subjects will be "Bronchial Asthma," "Pulmonary Emphysema and Fibrosis," "Applied Physiologic Therapy in Respiratory Disease" and "Pulmonary Edema."

Another out-of-state speaker who will lecture at the course is Dr. William S. Conklin of Portland, Oregon. Dr. Conklin will talk on "Surgical Therapy in Tuberculosis.

Dr. C. Richard Walmer, medical director of the Industrial Hygiene Foundation, Pittsburgh, Pennsylvania, has been named managing director of that organization. The Foundation operates under the auspices of the Mellon Institute. Dr. Walmer, who has been medical director of the Foundation and also a senior fellow of Mellon Institute since 1946, will now be an administrative fellow in the Institute.

Dr. Marcio M. Bueno, Fall River, Massachusetts, recently returned from a tour through Europe where he visited hospitals and medical schools in various countries. Upon invitation of Professor Lopo de Carvalho, Lisbon, Regent of the College for Portugal, Dr. Bueno lectured on "Treatment of Pulmonary Tuberculosis" before the faculty of medicine at the University of Lisbon.

Dr. D. E. Jenkins, Houston, Texas, presented a paper on "Recent Advances in the Treatment of Tuberculosis" at the Mid-South Regional Meeting of the American College of Physicians held in Memphis, January 12-13.

SEVENTH ANNUAL MEETING, AMERICAN COLLEGE OF ALLERGISTS

The Seventh Annual Meeting of the American College of Allergists will be held at the Edgewater Beach Hotel, Chicago, Illinois, February 12, 13 and 15. A post collegiate instructional course will be presented on the three days just preceding the annual meeting.

LABORATORY TRAINING COURSES

Five training courses on laboratory diagnosis of tuberculosis will be given by the Communicable Disease Center, U. S. Public Health Service, Chamblee, Georgia, during the year 1951. The courses are of one and two weeks duration and will be given on the following dates: April 16-27; April 30 to May 11; May 14-18; October 29 to November 2; and November 5-16. Information and application forms should be requested from the Officer in Charge, Laboratory Training Services, Communicable Disease Center, U. S. Public Health Service, P. O. Box 185, Chamblee, Georgia.

COLLEGE EVENTS

17th Annual Meeting, American College of Chest Physicians, Atlantic City, New Jersey, June 7-10, 1951.

Annual Meeting, New York State Chapter, New York City, February 8, 1951.

San Francisco Postgraduate Course, San Francisco, California, February 19-23, 1951.

Philadelphia Postgraduate Course, Philadelphia, Pennsylvania, March 26-30, 1951.

Milwaukee Postgraduate Course for General Practitioners, Milwaukee, Wisconsin, April, 1951.

Annual Meeting, Missouri Chapter, Kansas City, Missouri, April 22, 1951.

Obituary

BURT RUSSELL SHURLY

1871 - 1950

Dr. Burt S. Shurly was born in Chicago, Illinois on the Fourth of July, 1871 and died in Detroit, Michigan, where he had practiced medicine for over fifty years, on October 20, 1950. Dr. Shurly attended Western Military Academy and the University of Wisconsin. He received his degree of Doctor of Medicine from the Detroit College of Medicine in 1895, and did postgraduate work at the University of Vienna. He was a veteran of the Spanish-American War and in the First World War he organized and commanded Base Hospital No. 36 and was also stationed at Vittel, France. Dr. Shurly was decorated by the French Government and was also awarded the Legion of Honor and the Purple Heart.

Dr. Shurly was Professor of Otolaryngology, and at one time Dean of the Detroit College of Medicine. He was instrumental in having the College taken over as the Medical College of Wayne University. He was Consultant Otolaryngologist at Woman's, Harper and Receiving Hospitals.

He was a past-president of the American Laryngological, Rhinological and Otological Society, a Fellow and former member of the Board of Governors of the American College of Surgeons, a Fellow of the American Medical Association and member of the House of Delegates for 26 years. He supported the resolution for the establishment of a Section on Diseases of the Chest in the American Medical Association. Dr. Shurly was also a Fellow of the American College of Physicians and the American College of Chest Physicians.

After World War I, Dr. Shurly established the Shurly Hospital which he maintained until 1949. He was President of the Detroit Tuberculosis Sanatorium, and a member of the Board of the Detroit Board of Education for 23 years.

Dr. Shurly was a very remarkable personage. He distinguished himself not only in his chosen profession and specialty, but also as a soldier, educator, hospital organizer, civic leader and financier.

Willard Boyden Howes, M.D., Governor for Michigan.

NEW HEYDEN BROCHURE ON ANTIBIOTICS

The Heyden Chemical Corporation, 393 Seventh Avenue, New York 1, New York, has just issued a new 3-color illustrated brochure on Penicillin and Streptomycin—two of the most valuable antibiotics available to the medical, hospital, and biological fields, and which are manufactured at Heyden's ultra-modern plant at Princeton, New Jersey.

Copies of this important booklet, which gives facts and figures on various diseases and their treatment through penicillin or streptomycin, are available promptly upon request. Address your letter direct to Heyden's main offices, 393 Seventh Avenue, New York 1, New York.

MEDICAL SERVICE BUREAU

POSITIONS AVAILABLE

Superintendent and medical director wanted for 100 bed tuberculosis sanatorium in south-east Minnesota. Modern, well equipped. Full maintenance. Salary open. Address correspondence to Mr. Eldridge Peters, Chairman, Board of Directors, Mineral Springs Sanatorium, Cannon Falls, Minnesota.

Staff physicians wanted. Kentucky's new six hospital tuberculosis program needs physicians in staff capacity. Salary $5,000.00 per year plus maintenance. Eligibility for Kentucky licensure required. Contact T. F. Moore, Jr., Executive Director, State Tuberculosis Sanatorium Commission, Frankfort, Kentucky.

Resident on service approved for training in pulmonary diseases. Five-hundred bed county hospital with 130 sanatorium beds; large chest clinic. Recent graduate, one year residency or equivalent, preferred. Opportunity for surgical experience. Salary $235 monthly, increased to $450 September 1, 1951. Meals and laundry. Contact Director, Santa Clara County Sanatorium, San Jose, California.

POSITIONS WANTED

Physician, experienced, draft exempt, wants position as medical director of small, modern tuberculosis hospital. Fellow, American College of Chest Physicians. Please address Box 248B, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Experienced chest physician desires position in tuberculosis sanatorium. Educated and trained in Europe. Has first citizenship papers and is licensed to practice medicine in State of New York. References concerning experience and list of publications available. Please address Box 249B, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Position wanted as administrator of hospital or sanatorium. Experienced. References available. Please address Box 250B, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

WANTED TO BUY: Used Cutler Thoracoscope (Operating) complete. Dr. Paul H. Wedin, 207 Derby Building, Wichita, Kansas.

The Armour Laboratories' ACTH, which is non-allergenic and free of posterior pituitary factors, will be marketed hereafter under the brand name of Acthar, it was announced November 20th.

Acthar can now be dispensed by or on the prescription of a physician. It is available for ambulatory patients, and is no longer restricted to hospitalized patients.

In explaining the elimination of allergenic and posterior pituitary elements in Acthar, the Armour Laboartories pointed out that the adrenocorticotropic hormone is derived from the antelior lobe of the pituitary gland. In the manufacturing process, however, posterior pituitary factors and other undesirable proteins are carried over into crude ACTH. The posterior factors can cause cramps and other bad reactions, if they are present even in minute quantities. Other proteins in crude ACTH have been held responsible for allergies. Each lot of Acthar is submitted to six biological tests to make sure that it is free of post pituitary factors and other contaminating hormones and proteins.

As an example of dosage, it was stated that only one-third to one-fifth as much Acthar need be used for maintenance doses in rheumatoid arthritis as is required with adrenal hormone substitution preparations. In most cases, therefore, cost of Acthar to the patient is as low or less than that of a synethetic adrenal hormone.

Schatzalp Sanatorium Davos

Medical Director: GUSTAV MAURER, M.D., F.C.C.P.

"Schatzalp" *on a most beautiful and sunny mountain-plateau above* ***Davos*** *in the midst of the* ***Swiss Alps.***

The ***Leading Sanatorium*** *of* ***Switzerland*** *for* ***Diseases of the Chest.***

Daily "all-in"—terms, including ordinary medical treatment and nursing: from 7 to 10 Dollars.

Air-Journey from New York to Davos - - - - - 16 hours
from Rio de Janeiro to Davos - - - 29 hours

For further particulars please apply to the
SCHATZALP ADMINISTRATION, DAVOS SWITZERLAND

ALUM ROCK SANATORIUM

SAN JOSE, CALIFORNIA
TELEPHONE CLAYBURN 8-4921

A Non-profit sanatorium for the treatment of tuberculosis and other diseases of the chest.

Visiting Medical Staff:

Cabot Brown, M.D., San Francisco
Gerald L. Crenshaw, M.D., Oakland
J. Lloyd Eaton, M.D., Oakland
Ina Gourley, M.D., Oakland
H. Corwin Hinshaw, M.D., San Francisco
W. Dale Peterson, M.D., Oakland
Glenroy N. Pierce, M.D., San Francisco
Harold Guyon Trimble, M.D., Oakland
James Robert Wood, M.D., Oakland

Medical Director
Buford H. Wardrip, M.D.
Telephone Clayburn 8-4921

Associate Medical Director
C. Gerald Scarborough, M.D.

Consulting Pathologist
E. Gwyn Roberts, M.D., San Francisco

100 Beds for Crippled Children *200 Beds for Tuberculosis*

ST. JOHNS SANITARIUM, Springfield, Ill.

Complete in every detail. Rates low—because of the services of the Hospital Sisters of St. Francis.

Medical Director
DR. ROBERT K. CAMPBELL

Address
SISTER THEODINE, R.N., Supt.

Cragmor Sanatorium

For the treatment of tuberculosis and diseases of the chest, situated near Colorado Springs in the heart of the Rockies. Ideal year-round climate. Individual apartments, with or without baths. Rates on request.

For detailed information address
Henry W. Maly, M.D., Director
Cragmor Sanatorium
Colorado Springs, Colorado

Unsurpassed year-round climate
Near but not upon the desert
Altitude 2350 feet

Southern Sierras Sanatorium

For Chest Diseases

BANNING, CALIFORNIA

90 miles east of Los Angeles on Highways 99, 60 and 70

Quiet contentment
Absence of hospital atmosphere
Sustained reputation for satisfaction

C. E. ATKINSON, M.D., *Medical Director*

SOUTHWESTERN PRESBYTERIAN SANATORIUM

ALBUQUERQUE,
NEW MEXICO

★

A well-equipped Sanatorium in the Heart of the Well Country.

Write for Information and Rates

MARYKNOLL SANATORIUM

MONROVIA, CALIFORNIA

(MARYKNOLL SISTERS)

A sanatorium for the treatment of tuberculosis and other diseases of the lungs. Located in the foothills of the Sierra Madre Mountains. Southern exposure. Accommodations are private, modern and comfortable. General care of patient is conducive to mental and physical well being.

SISTER MARY EDWARD
Superintendent

E. W. HAYES, M.D.
Medical Director

SANATORIUM DIRECTORY

The sanatoria listed in this section are among the finest sanatoria in the United States. They are prepared to offer private, individual, specialized care to your patients.

•

For listings in the SANATORIUM DIRECTORY write to the American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois

ALUM ROCK SANATORIUM
San Jose, California

CALIFORNIA SANATORIUM
Belmont, California

CRAGMORE SANATORIUM
Colorado Springs, Colorado

EUDOWOOD SANATORIUM
Towson, Maryland

MARYKNOLL SANATORIUM
Monrovia, California

PALMER SANATORIUM
Springfield, Illinois

ROCKY GLEN SANATORIUM
McConnelsville, Ohio

SCHATZALP SANATORIUM DAVOS
Davos, Switzerland

ST. JOHNS SANITARIUM
Springfield, Illinois

SOUTHERN SIERRAS SANATORIUM
Banning, California

SOUTHWESTERN PRESBYTERIAN SANATORIUM
Albuquerque, New Mexico

THE SAMUEL AND NETTIE BOWNE HOSPITAL
Poughkeepsie, New York

SANATORIO ALBERTAL
Buenos Aires, Argentina

SANATORIO SAN ANGEL
Mexico City, Mexico

SWEDISH NATIONAL SANATORIUM
Englewood (Denver) Colorado
Modern Equipment — Moderate Prices

NOTICE TO SUBSCRIBERS

DISEASES OF THE CHEST IS NOW PUBLISHED MONTHLY

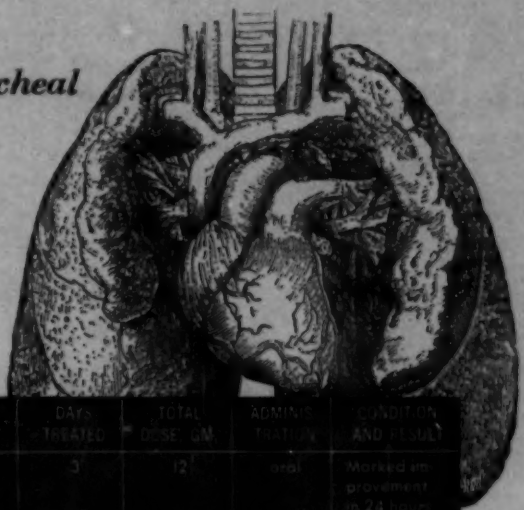
NEW SUBSCRIPTION RATES FOR TWELVE (12) ISSUES

United States of America	$8.50 per year
All other countries	$9.50 per year
Back issues	$1.00 per copy
Special issues (December, 1949)	$2.00 per copy

Jay Arthur Myers, M.D., F.C.C.P., Chairman, Editorial Board.

When writing please mention *Diseases of the Chest*

in acute laryngotracheal bronchitis prompt response with Terramycin



CASE	DIAGNOSIS	ORGANISM	DAYS TREATED	TOTAL DOSE GM.	ADMINISTRATION	CONDITION AND RESULT
16	Acute laryngotracheal bronchitis	Hemophilus influenzae	3	12	oral	Marked improvement in 24 hours. Recovery

Case report taken from Herrell, W. E.; Heilman, F. R., and Wellman, W. E.: Ann. New York Acad. Sc. 53:448 (Sept. 15) 1950.

CRYSTALLINE Terramycin HYDROCHLORIDE

Rapidly Absorbed

"... produces significant continuous blood levels when 250 mg. are given every six hours."[1]

Well Tolerated

"The drug is tolerated by mouth and no serious side-reactions occur."[2]

Dosage: On the basis of findings obtained in over 150 leading medical research centers, 2 Gm. daily by mouth in divided doses q. 6 h. is suggested for most acute infections.

Supplied: 250 mg. capsules, bottles of 16 and 100;
100 mg. capsules, bottles of 25 and 100;
50 mg. capsules, bottles of 25 and 100.

1. Welch, H.; Hendricks, F. D.; Price, C. W., and Randall, W. A.: J. A. Ph. A. (Sc. Ed.) 39:185 (Apr.) 1950.
2. Douglas, R. G.; Ball, T. L., and Davis, I. F.: California Med. 73:463 (Dec.) 1950.

Pfizer

Antibiotic Division
CHAS. PFIZER & CO., INC.
Brooklyn 6, N.Y.

EFFERVESCENT "PARASAL" TABLETS

... the logical solution to the many problems of P. A. S. administration

In the P.A.S. therapy of tuberculosis, EFFERVESCENT PARASAL TABLETS —newest of Panray's formulations— are fast becoming the preferred dosage form for children and adults. One tablet dropped into water effervesces and dissolves almost instantly, providing 2 grams of active Parasal in a pleasantly-flavored, clear solution.

GREATER ACCEPTABILITY to the PATIENT: EFFERVESCENT PARASAL TABLETS are pleasantly mint flavored. They can be taken in water, milk, or fruit juices. And the patient need no longer swallow a huge number of tablets every day. Just 1½ tablets q.i.d. is sufficient to give the average dose of 12 gms. daily.

GREATER CONVENIENCE: Now you need no longer worry about time-consuming filtrations, storage problems, decomposition of solutions, etc. EFFERVESCENT PARASAL TABLETS, bisected for even greater convenience, *always and instantly provide a fresh, fully potent solution.*

GREATER ECONOMY: EFFERVESCENT PARASAL TABLETS eliminate the high costs of extra labor . . . wasted batches

. . . refrigeration . . . time-consuming calculations. You simply use tablets as needed. Yet the equivalent cost is no higher than that of other Parasal dosage forms.

MORE ACTIVITY PER TABLET: EFFERVESCENT PARASAL TABLETS have the highest potency of any P.A.S. tablet yet produced. Each tablet contains 2 grams of active Parasal, *4 times as much as any Parasal tablet designed for oral ingestion.*

MORE RAPID ABSORPTION: Since the patient ingests a solution rather than tablets or granules, it is almost certain that the drug will be rapidly and completely absorbed. *Samples and prices on request.*

DOSAGE: 1½ tablets q.i.d.,— or as you prescribe.

THE Panray CORP.

240 CANAL STREET, NEW YORK 13, NEW YORK